

# Exhibit Q

Kelly Tuttle, Ph.D.

Page 1

IN THE UNITED STATES DISTRICT COURT  
FOR THE EASTERN DISTRICT OF NEW JERSEY

----- )  
IN RE JOHNSON & JOHNSON )  
TALCUM POWDER PRODUCTS )  
MARKETING, SALES ) MDL NO.  
PRACTICES, AND PRODUCTS ) 16-2738 (FLW) (LHG)  
LIABILITY LITIGATION )  
 )  
----- )  
 )  
THIS DOCUMENT RELATES TO )  
ALL CASES )  
 )  
-----

— — —  
Thursday, April 11, 2019  
— — —

Videotaped Deposition of KELLY TUTTLE,  
Ph.D., held at the Hilton Fort Worth,  
815 Main Street, Fort Worth, Texas,  
commencing at 9:08 a.m., on the above date,  
before Michael E. Miller, Certified Court  
Reporter, Registered Diplomate Reporter,  
Certified Realtime Reporter and Notary  
Public.

— — —  
GOLKOW LITIGATION SERVICES  
877.370.3377 ph | fax 917.591.5672  
deps@golkow.com

Kelly Tuttle, Ph.D.

Page 2	Page 4
<p>1 APPEARANCES:</p> <p>2 LUNDY LUNDY SOILEAU &amp; SOUTH, LLP</p> <p>3 BY: RUDIE R. SOILEAU, JR., ESQUIRE</p> <p>4 rudiesoileau@gmail.com</p> <p>5 KRISTIE M. HIGHTOWER, ESQUIRE</p> <p>6 khightower@lundyallllp.com</p> <p>7 501 Broad Street</p> <p>8 Lake Charles, Louisiana 70801</p> <p>9 (337) 802-4352</p> <p>10 Counsel for Plaintiffs' Steering</p> <p>11 Committee</p> <p>12</p> <p>13 BEASLEY ALLEN, PC</p> <p>14 BY: P. LEIGH O'DELL, ESQUIRE</p> <p>15 leigh.odell@beasleyallen.com</p> <p>16 218 Commerce Street</p> <p>17 Montgomery, Alabama 36103-4160</p> <p>18 (334) 269-2343</p> <p>19 Counsel for Plaintiffs' Steering</p> <p>20 Committee</p> <p>21</p> <p>22 ASHCRAFT &amp; GEREL LLP</p> <p>23 BY: MICHELLE PARFITT, ESQUIRE</p> <p>24 mparfi@aol.com</p> <p>4900 Seminary Road</p> <p>Suite 650</p> <p>Alexandria, Virginia 22311</p> <p>(703) 931-5500</p> <p>Counsel for Plaintiffs' Steering</p> <p>Committee</p> <p>TUCKER ELLIS LLP</p> <p>BY: MICHAEL C. ZELLERS, ESQUIRE</p> <p>michael.zellers@tuckerellis.com</p> <p>515 South Flower Street</p> <p>42nd Floor</p> <p>Los Angeles, California 90071</p> <p>(213) 430-3400</p> <p>Counsel for Johnson &amp; Johnson</p> <p>Defendants</p>	<p>1 INDEX</p> <p>2</p> <p>3 APPEARANCES 2</p> <p>4</p> <p>5 PROCEEDINGS 8</p> <p>6</p> <p>7 EXAMINATION OF KELLY TUTTLE, Ph.D.:</p> <p>8 BY MR. SOILEAU 8</p> <p>9</p> <p>10 CERTIFICATE 432</p> <p>11 ERRATA 434</p> <p>12 ACKNOWLEDGMENT OF DEPONENT 435</p> <p>13 LAWYER'S NOTES 436</p> <p>14</p> <p>15</p> <p>16</p> <p>17</p> <p>18</p> <p>19</p> <p>20</p> <p>21</p> <p>22</p> <p>23</p> <p>24</p>
Page 3	Page 5
<p>1 APPEARANCES:</p> <p>2 DRINKER BIDDLE &amp; REATH, LLP</p> <p>3 BY: JACK N. FROST, JR., ESQUIRE</p> <p>4 jack.frost@dbr.com</p> <p>5 600 Campus Drive</p> <p>6 Florham Park, New Jersey 07932</p> <p>7 (973) 549-7000</p> <p>8 Counsel for Johnson &amp; Johnson</p> <p>9 Defendants</p> <p>10</p> <p>11 TUCKER ELLIS LLP</p> <p>12 BY: MICHAEL ANDERTON, ESQUIRE</p> <p>13 michael.anderton@tuckerellis.com</p> <p>14 950 Main Avenue, Suite 1100</p> <p>15 Cleveland, Ohio 44113-7213</p> <p>16 (216) 696-3675</p> <p>17 Counsel for PTI Royston LLC and PTI</p> <p>18 Union LLC</p> <p>19</p> <p>20 SEYFARTH SHAW, LLP</p> <p>21 BY: REBECCA WOODS, ESQUIRE</p> <p>22 rwoods@seyfarth.com</p> <p>23 975 F Street, N.W.</p> <p>24 Washington, D.C. 20004-1454</p> <p>(202) 463-2400</p> <p>Counsel for Personal Care Products</p> <p>ALSO PRESENT:</p> <p>DEBBIE DRONETT, Paralegal</p> <p>VIDEOGRAPHER:</p> <p>DAVID LANE,</p> <p>Golkow Litigation Services</p>	<p>1 DEPOSITION EXHIBITS</p> <p>2 KELLY TUTTLE, Ph.D.</p> <p>3 April 11, 2019</p> <p>4 NUMBER DESCRIPTION PAGE</p> <p>5 Tuttle-1 Tuttle Expert Report 9</p> <p>6 Tuttle-2 Tuttle Previous Four Years 12</p> <p>7 Testimony</p> <p>8</p> <p>9 Tuttle-3 Chapter from Reference 17</p> <p>10 Guide on Toxicology</p> <p>11 Tuttle-4 Excerpt from The Basic 20</p> <p>12 Science of Poisons</p> <p>13</p> <p>14 Tuttle-5 Tuttle Curriculum Vitae 26</p> <p>15</p> <p>16 Tuttle-6 21 C.F.R. 740 50</p> <p>17</p> <p>18 Tuttle-7 1965 Hill Publication 72</p> <p>19</p> <p>20 Tuttle-8 Excerpt from Modern 82</p> <p>21 Toxicology Third Edition</p> <p>22 Tuttle-9 CTEH Billing Summary 93</p> <p>23 Tuttle-10 CTEH Billing Summary 93</p> <p>24 Tuttle-11 Tuttle Supplemental 102</p> <p>Materials Reviewed and</p> <p>Considered</p> <p>Tuttle-12 Excerpt from IARC 141</p> <p>Monograph 93</p> <p>Tuttle-13 Egli and Newton Publication 157</p> <p>Tuttle-14 1971 Henderson et al 159</p> <p>Publication</p> <p>Tuttle-15 1979 Venter et al 164</p> <p>Publication</p>

2 (Pages 2 to 5)

Kelly Tuttle, Ph.D.

Page 6	Page 8
<p>1 DEPOSITION EXHIBITS</p> <p>2 Tuttle-16 1986 Henderson et al 166</p> <p>3 Publication</p> <p>4 Tuttle-17 2004 Kissler et al 170</p> <p>5 Publication</p> <p>6 Tuttle-18 2004 Sj?sten et al 172</p> <p>7 Publication</p> <p>8 Tuttle-19 2019 McDonald et al 174</p> <p>9 Publication</p> <p>10 Tuttle-20 Ovarian Cancer Prevention 197</p> <p>11 (PDR) Patient Information</p> <p>12 Tuttle-21 Health Canada Draft 201</p> <p>13 Screening Assessment</p> <p>14 Tuttle-22 2004 Fax Transmission of 217</p> <p>15 Sj?sten Publication</p> <p>16 Tuttle-23 4/1/14 FDA Letter 224</p> <p>17 Tuttle-24 1994 Wehner Publication 249</p> <p>18 Tuttle-25 3/17/97 Wehner Letter 261</p> <p>19 Tuttle-26 Handwritten Statement 273</p> <p>20 Tuttle-27 9/17/97 Wehner Letter 280</p> <p>21 Tuttle-28 Appendix C to Tuttle Expert 284</p> <p>22 Report</p> <p>23 Tuttle-29 10/7/04 Wehner Letter 293</p> <p>24 Tuttle-30 2014 Nony et al Publication 320</p> <p>Tuttle-31 2/17/77 Schneider Letter 340</p>	<p>1 PROCEEDINGS</p> <p>2 (April 11, 2019 at 9:08 a.m.)</p> <p>3 THE VIDEOGRAPHER: We're now on</p> <p>4 the record. My name is David Lane,</p> <p>5 videographer for Golkow Litigation</p> <p>6 Services. Today's date is April 11th,</p> <p>7 2019. The time is 9:08 a.m.</p> <p>8 This deposition is taking place</p> <p>9 in Fort Worth, Texas, in the matter of</p> <p>10 Talcum Powder Litigation MDL. Our</p> <p>11 deponent today is Kelly Tuttle Ph.D.</p> <p>12 Our counsel will be noted on the</p> <p>13 stenographic record.</p> <p>14 The court reporter today is</p> <p>15 Mike Miller, who will now swear in the</p> <p>16 witness.</p> <p>17 KELLY TUTTLE, Ph.D.,</p> <p>18 having been duly sworn,</p> <p>19 testified as follows:</p> <p>20 BY MR. SOILEAU:</p> <p>21 Q. Good morning, Dr. Tuttle.</p> <p>22 A. Good morning.</p> <p>23 Q. I am Rudie Soileau. We met</p> <p>24 just a few moments ago. I'm an attorney from</p>
Page 7	Page 9
<p>1 DEPOSITION EXHIBITS</p> <p>2 Tuttle-32 Health Canada Risk 348</p> <p>3 Assessment Framework Study</p> <p>4 Tuttle-33 Global Harmonized System of 351</p> <p>5 Classification and Labeling</p> <p>6 of Chemicals</p> <p>7 Tuttle-34 IARC Monograph on Asbestos 362</p> <p>8 Tuttle-35 Listing of BioVentures 386</p> <p>9 Spinoff Companies</p> <p>10 Tuttle-36 NTP Study, Toxicology and 398</p> <p>11 Carcinogenesis Studies of</p> <p>12 Talc</p> <p>13 Tuttle-37 2016 Schildkraut et al 415</p> <p>14 Publication</p> <p>15 Tuttle-38 Article, Retire Statistical 419</p> <p>16 Significance</p> <p>17</p> <p>18</p> <p>19</p> <p>20</p> <p>21</p> <p>22</p> <p>23</p> <p>24</p>	<p>1 Lake Charles, Louisiana. I'm appearing today</p> <p>2 on behalf of women and the families of women</p> <p>3 who maintain that the use of Johnson &amp;</p> <p>4 Johnson talcum powder products led to the</p> <p>5 development of ovarian cancer.</p> <p>6 (Whereupon, Deposition Exhibit</p> <p>7 Tuttle-1, Tuttle Expert Report, was</p> <p>8 marked for identification.)</p> <p>9 BY MR. SOILEAU:</p> <p>10 Q. Let me begin by handing you an</p> <p>11 exhibit that I have marked as Tuttle</p> <p>12 Exhibit 1 and ask you to identify that for</p> <p>13 me.</p> <p>14 A. This is the report that I</p> <p>15 drafted regarding this litigation.</p> <p>16 Q. Very good. You understand that</p> <p>17 you are under oath today?</p> <p>18 A. I do.</p> <p>19 Q. And you have been deposed</p> <p>20 previously?</p> <p>21 A. Yes, I have.</p> <p>22 Q. Dr. Tuttle, I intend for all of</p> <p>23 my questions today to be clear and fair. If</p> <p>24 a question is for any reason not clear to you</p>



Kelly Tuttle, Ph.D.

<p style="text-align: right;">Page 10</p> <p>1 or if it does not seem fair, tell me. And if</p> <p>2 you tell me that, I'll do whatever is</p> <p>3 necessary to make sure that my questions seem</p> <p>4 clear and fair, okay?</p> <p>5 A. Sounds good.</p> <p>6 Q. If you do not say anything, I'm</p> <p>7 going to assume that my questions are clear</p> <p>8 and you are answering the question I've</p> <p>9 asked. Fair enough?</p> <p>10 A. Yes.</p> <p>11 MR. FROST: Rudie, I just have</p> <p>12 one question on the report. I just</p> <p>13 want to make sure it's purposeful. I</p> <p>14 note that the appendices are not in</p> <p>15 the back of the one that's marked as</p> <p>16 Exhibit 1. I just want to make sure</p> <p>17 that's purposeful.</p> <p>18 MR. SOILEAU: Yes.</p> <p>19 MR. FROST: Okay.</p> <p>20 MR. SOILEAU: I included the</p> <p>21 entire -- and let me ask the doctor.</p> <p>22 BY MR. SOILEAU:</p> <p>23 Q. Exhibit 1 is the entirety of</p> <p>24 the report itself as well as your references,</p>	<p style="text-align: right;">Page 12</p> <p>1 appendices that counsel referred to a moment</p> <p>2 ago.</p> <p>3 (Whereupon, Deposition Exhibit</p> <p>4 Tuttle-2, Tuttle Previous Four Years</p> <p>5 Testimony, was marked for</p> <p>6 identification.)</p> <p>7 BY MR. SOILEAU:</p> <p>8 Q. I've marked this document as</p> <p>9 Tuttle Exhibit 2. Do you recognize that?</p> <p>10 A. Yes, I do.</p> <p>11 Q. Do each of the instances listed</p> <p>12 in Appendix E, which is now Tuttle Exhibit 2,</p> <p>13 arise from a release, a spill or some other</p> <p>14 unintended event?</p> <p>15 A. No, they do not.</p> <p>16 Q. Which one does not?</p> <p>17 A. Let's see. There are several</p> <p>18 on here that are related to a spill or</p> <p>19 release or emergency response, and then there</p> <p>20 are others that are toxic tort litigation.</p> <p>21 Q. Which of the captions that are</p> <p>22 listed on Tuttle Exhibit 2 involve toxic tort</p> <p>23 litigation?</p> <p>24 A. So I'll just start at the</p>
<p style="text-align: right;">Page 11</p> <p>1 but none of the appendices, correct?</p> <p>2 MR. FROST: Didn't mean to</p> <p>3 interrupt your flow. I just wanted to</p> <p>4 make sure that that was on purpose.</p> <p>5 MR. SOILEAU: That's fine.</p> <p>6 A. cursory glance through, yes,</p> <p>7 this appears to be my complete report, with</p> <p>8 the exception of the appendices.</p> <p>9 BY MR. SOILEAU:</p> <p>10 Q. Very good.</p> <p>11 Were you asked, Doctor, by the</p> <p>12 attorneys for Johnson &amp; Johnson to review</p> <p>13 available information and offer an opinion</p> <p>14 addressing any relationship between Johnson &amp;</p> <p>15 Johnson talcum powder products and ovarian</p> <p>16 cancer?</p> <p>17 A. I was asked by attorneys to</p> <p>18 look at the scientific literature and the</p> <p>19 body of science to determine whether the body</p> <p>20 of science supports a causal association</p> <p>21 between perineal talcum powder exposure and</p> <p>22 ovarian cancer.</p> <p>23 Q. Very good.</p> <p>24 Let me show you one of the</p>	<p style="text-align: right;">Page 13</p> <p>1 beginning. The first one, Baukholt v.</p> <p>2 A.O. Smith. The second one, Wilson v.</p> <p>3 Eighty-Eight Oil. The third, Readwin v.</p> <p>4 Aurora Pumps. Then going to the fifth,</p> <p>5 Hudson v. Covestro. Then going to the second</p> <p>6 page, the second one, Messel v. Aurora Pump;</p> <p>7 the third, Howe v. Aurora Pump; and the</p> <p>8 fourth, Bradd v. Aurora Pump.</p> <p>9 Q. Do the four matters that</p> <p>10 reference Aurora Pump all involve the same</p> <p>11 issue generally from the perspective of a</p> <p>12 toxicologist?</p> <p>13 A. Yes, generally.</p> <p>14 Q. And what was the substance or</p> <p>15 agent involved in the four Aurora Pump cases?</p> <p>16 A. Those were involved in asbestos</p> <p>17 litigation.</p> <p>18 Q. Were the plaintiffs in the</p> <p>19 Aurora Pump litigations that are listed on</p> <p>20 Tuttle Exhibit 2 workers who had been</p> <p>21 occupationally exposed to asbestos?</p> <p>22 A. I would have to go back and</p> <p>23 look at the individual cases. I don't</p> <p>24 recall.</p>

4 (Pages 10 to 13)

Kelly Tuttle, Ph.D.

Page 14	Page 16
<p>1 Q. Okay. The Baukholt matter, the 2 first one listed on Exhibit 2, what did that 3 litigation involve? 4 A. That also was asbestos 5 litigation. 6 Q. And what about Wilson v. 88 7 Oil? 8 A. That involved a number of 9 potential industrial hygiene and 10 toxicological exposures resulting from an oil 11 transloading facility. 12 Q. Hudson, which is also on the 13 first page of Tuttle Exhibit 2, what was the 14 agent or substance at issue in the Hudson 15 matter, Doctor? 16 A. Hudson v. Covestro involved 17 spray foam insulation. 18 Q. Was there any allegation that 19 the spray foam included as a constituent 20 asbestos fibers? 21 A. No. 22 Q. Okay. Have you ever been asked 23 to review available information and offer an 24 expert opinion involving a manufactured</p>	<p>1 consider Johnson &amp; Johnson the manufacturer 2 of the talcum powder products that we are 3 discussing today? 4 MR. FROST: Objection. 5 A. So I was asked to review the 6 body of science and the scientific 7 literature, and so in regards to the 8 scientific literature, a lot of the studies 9 and things are -- do not specify what form of 10 talcum powder is involved in their studies or 11 in their assessments, so this is an 12 assessment of the body of science as a whole. 13 BY MR. SOILEAU: 14 Q. I see. 15 So from your perspective, has 16 the work that you've done in this case 17 focused on the body of science and not the 18 actual products that Johnson &amp; Johnson sells 19 to citizen consumers? 20 MR. FROST: Objection. 21 A. Well, as I said, I assessed the 22 body of science, and a large number of 23 studies do not specify the type of talcum 24 powder. That being said, there are examples</p>
Page 15	Page 17
<p>1 retail product other than this case? 2 A. In regards to litigation, not 3 that I recall specifically. I guess the 4 spray foam insulation would be considered a 5 manufactured product. 6 Q. But not one sold retail, 7 correct? 8 A. Not that I can recall, no. 9 Q. The product that we're talking 10 about now, talcum powder products, you 11 understand those were manufactured by 12 Johnson &amp; Johnson? 13 MR. FROST: Objection. 14 BY MR. SOILEAU: 15 Q. Is that your understanding? 16 A. My understanding is that talcum 17 powder is -- or talc specifically is 18 naturally occurring and is sold in any number 19 of options. In this particular case my 20 research is around perineal talcum powder and 21 it is my understanding that Johnson &amp; Johnson 22 sells talcum powder products. 23 Q. From your perspective and your 24 work in this case, would it be appropriate to</p>	<p>1 such as the FDA and others where Johnson &amp; 2 Johnson products specifically were tested or 3 examined. 4 But in regards to 5 epidemiologically or otherwise, it revolves 6 around talcum powder products as a whole and 7 the scientific literature as a whole. 8 BY MR. SOILEAU: 9 Q. Do you agree that the essence 10 of toxicology is the study of adverse effects 11 of agents on organisms? 12 A. Toxicology is the study of the 13 dose and response of various products, either 14 man-made or natural, and their potential 15 adverse effects on the environment, on the 16 human body, on animals. 17 (Whereupon, Deposition Exhibit 18 Tuttle-3, Chapter from Reference Guide 19 on Toxicology, was marked for 20 identification.) 21 BY MR. SOILEAU: 22 Q. Let me show you an additional 23 exhibit. I've marked this as Exhibit 3. 24 This is a chapter from the reference manual</p>

5 (Pages 14 to 17)

Kelly Tuttle, Ph.D.

<p style="text-align: right;">Page 18</p> <p>1 that is noted in your report and included in</p> <p>2 your reference materials.</p> <p>3 Do you recognize this chapter?</p> <p>4 A. Yes.</p> <p>5 Q. Do you have a copy of the</p> <p>6 reference manual somewhere at home or in your</p> <p>7 office?</p> <p>8 A. It's in our corporate office in</p> <p>9 Little Rock, Arkansas, yes.</p> <p>10 Q. Where do you office?</p> <p>11 A. I office out of my home here</p> <p>12 outside of Fort Worth.</p> <p>13 Q. I see.</p> <p>14 Turn to page 636, if you would.</p> <p>15 I'm going to put this on the ELMO as well,</p> <p>16 but I'm focusing on the second full paragraph</p> <p>17 on page 636, and the second sentence which</p> <p>18 says: It -- referring to toxicology -- it is</p> <p>19 the study of the adverse effects of chemical</p> <p>20 and physical agents on living organisms.</p> <p>21 Did I read that correctly?</p> <p>22 A. Yes, you read that correctly.</p> <p>23 Q. Do you agree with that</p> <p>24 statement?</p>	<p style="text-align: right;">Page 20</p> <p>1 (Whereupon, Deposition Exhibit</p> <p>2 Tuttle-4, Excerpt from The Basic</p> <p>3 Science of Poisons, was marked for</p> <p>4 identification.)</p> <p>5 BY MR. SOILEAU:</p> <p>6 Q. I'll mark this as Exhibit 4.</p> <p>7 This is a one-page excerpt from a textbook.</p> <p>8 The cover of the textbook is on the first</p> <p>9 page.</p> <p>10 You recognize that textbook?</p> <p>11 A. Yes, I do.</p> <p>12 Q. This is the ninth edition, I</p> <p>13 believe, but you cite the eighth edition as a</p> <p>14 textbook in your reference manual, correct?</p> <p>15 A. Yes. The ninth edition is</p> <p>16 brand-new. I actually just received it the</p> <p>17 other day.</p> <p>18 Q. I see.</p> <p>19 Do you consider the Casarett &amp;</p> <p>20 Doull textbook on toxicology to be a</p> <p>21 generally accepted and authoritative textbook</p> <p>22 for the field of toxicology?</p> <p>23 A. I think as I state in my</p> <p>24 report, Casarett &amp; Doull's is a commonly used</p>
<p style="text-align: right;">Page 19</p> <p>1 A. As I said, toxicology is the</p> <p>2 study of compounds and their potential for</p> <p>3 adverse health effects on living organisms as</p> <p>4 well as the environment.</p> <p>5 Q. Is that a yes to my question?</p> <p>6 A. Well, again, I said that</p> <p>7 toxicology is the study of the potential</p> <p>8 adverse health effects of chemicals, be them</p> <p>9 man-made or naturally occurring, on living</p> <p>10 organisms, including the environment.</p> <p>11 Q. Yes, Doctor. I did hear your</p> <p>12 answer, but my question was: Do you agree</p> <p>13 with the summary statement that I read from</p> <p>14 the reference manual, Tuttle Exhibit 3?</p> <p>15 MR. FROST: Objection.</p> <p>16 A. Again, as I said, in addition,</p> <p>17 I said that toxicology is the study of</p> <p>18 adverse effects of chemical and physical</p> <p>19 agents, be them natural or man-made, on</p> <p>20 living organisms, that includes animals and</p> <p>21 the environment.</p> <p>22 BY MR. SOILEAU:</p> <p>23 Q. Let me show you another exhibit</p> <p>24 then.</p>	<p style="text-align: right;">Page 21</p> <p>1 toxicological textbook in teaching and</p> <p>2 education for toxicology.</p> <p>3 Q. Do you consider it</p> <p>4 authoritative for your work as a</p> <p>5 toxicologist?</p> <p>6 MR. FROST: Objection.</p> <p>7 A. Again, it's commonly used for</p> <p>8 teaching toxicological principles. As far as</p> <p>9 being authoritative, that's very general.</p> <p>10 Casarett &amp; Doull's covers a wide range of</p> <p>11 topics and a wide range of toxicological</p> <p>12 principles. I couldn't say specifically,</p> <p>13 without getting into some specifics in the</p> <p>14 textbook, on whether it would be</p> <p>15 authoritative or not, but it is commonly used</p> <p>16 for teaching toxicological principles.</p> <p>17 BY MR. SOILEAU:</p> <p>18 Q. Right. Doctor, we're not, of</p> <p>19 course, teaching today, at least that's not</p> <p>20 our primary purpose. We're here today to</p> <p>21 discuss your expert testimony.</p> <p>22 I need to ask you: Do you</p> <p>23 consider it to be reliance material for your</p> <p>24 work as a toxicologist?</p>

6 (Pages 18 to 21)

Kelly Tuttle, Ph.D.

<p style="text-align: right;">Page 22</p> <p>1 A. I cite Casarett &amp; Doull's in my 2 report regarding toxicological principles. I 3 certainly refer to it. I also refer to the 4 science that it cites and the basis for what 5 it includes in the textbook. 6 Q. Let's look at page 2 of Tuttle 7 Exhibit 4. In the first paragraph, the third 8 sentence, I want to put it on the ELMO and 9 read it: Toxicology arose as a way to 10 understand, prevent, mitigate and treat the 11 potentially harmful consequences of many of 12 the substances we are exposed to. 13 Did I read that correctly? 14 A. Yes, you read that correctly. 15 Q. Do you agree with that 16 statement from the Casarett text? 17 A. I have not -- as I said 18 earlier, this is the new edition, which I 19 haven't -- I'm not versed in, I haven't read. 20 I just received it. 21 Without going into more detail, 22 I can't say whether I agree or disagree. 23 Q. So you're not able to agree or 24 disagree with this statement? Just to be</p>	<p style="text-align: right;">Page 24</p> <p>1 the study of potential adverse effects of 2 agents, be them natural or man-made, on 3 living organisms and the environment. 4 Q. Do you agree that the science 5 of toxicology includes the prevention of 6 adverse effects? 7 A. It depends. You know, I 8 believe that classically and I think it even 9 said in the reference manual we discussed 10 earlier that toxicology is the study of 11 poisons. A lot of that revolves around dose 12 and understanding the role of dose in 13 exposures to products. 14 It certainly can be involved in 15 the prevention of adverse effects. 16 Q. I asked if you agree that the 17 science of toxicology includes the prevention 18 of adverse effects and you said in part, it 19 depends. What does it depend on? 20 MR. FROST: Objection. 21 A. Well, as I said, you know, 22 classically, and then the key tenet of 23 toxicology is the dose makes the poison. The 24 dose plays a key role in assessing whether an</p>
<p style="text-align: right;">Page 23</p> <p>1 clear, I'm not asking you if it actually 2 appears in the ninth edition. I'm simply 3 asking you if this statement, which I have 4 read to you from the ninth edition, is a 5 statement that you can agree with. 6 A. Well, as I said, I -- without 7 reading more in, and I'm not familiar with 8 this new edition of the textbook, I haven't 9 reviewed it, I can't agree or disagree. 10 Q. All right. Let me ask you 11 about another statement. Just below the 12 statement that I read is a statement that is 13 in italics. And it says: Toxicology is the 14 study of adverse effects of chemical, 15 physical or biological agents on living 16 organisms and the ecosystem, including the 17 prevention and amelioration of such adverse 18 effects. 19 Can you agree or disagree with 20 that statement? 21 A. Well, again, that's the 22 definition of toxicology as described in the 23 textbook, and I believe that's an iteration 24 of what I said earlier about toxicology being</p>	<p style="text-align: right;">Page 25</p> <p>1 agent can be harmful or have a potential 2 adverse effect. 3 So depending on the scenarios 4 of the questions being asked or how 5 toxicology is being applied, it can certainly 6 be involved in the prevention of or the 7 research to prevent the adverse effects. 8 BY MR. SOILEAU: 9 Q. Do you recognize the second 10 statement I read, the italicized paragraph 11 from the Casarett textbook? 12 MR. FROST: Objection. 13 A. I'm sorry, it's stated here in 14 this new edition of the Casarett textbook. 15 BY MR. SOILEAU: 16 Q. Yes. Do you recognize it 17 independent of the textbook? 18 A. Not specifically, no. 19 Q. Do you see in the second 20 paragraph from that page, just above the 21 quoted language, it says According to the 22 Society of Toxicology? 23 A. Yes, I do. 24 Q. You recognize that entity that</p>

7 (Pages 22 to 25)

Kelly Tuttle, Ph.D.

<p style="text-align: right;">Page 26</p> <p>1 is the Society of Toxicology?</p> <p>2 A. I do. I'm a member of the</p> <p>3 Society of Toxicology.</p> <p>4 Q. Right. That's what I was going</p> <p>5 to ask.</p> <p>6 Let me go ahead and show you</p> <p>7 what I will mark as Tuttle Exhibit 5.</p> <p>8 (Whereupon, Deposition Exhibit</p> <p>9 Tuttle-5, Tuttle Curriculum Vitae, was</p> <p>10 marked for identification.)</p> <p>11 BY MR. SOILEAU:</p> <p>12 Q. An additional attachment to</p> <p>13 your report. Do you recognize this?</p> <p>14 A. Yes, I do.</p> <p>15 Q. Is this essentially your CV?</p> <p>16 A. Yes.</p> <p>17 Q. And it includes, as you just</p> <p>18 noted, your membership in the Society of</p> <p>19 Toxicology or SOT, the same entity that is</p> <p>20 referenced in this excerpt from Casarett,</p> <p>21 which is Tuttle Exhibit 4, correct?</p> <p>22 A. Yes, that's correct.</p> <p>23 Q. Separate from the case that</p> <p>24 brings us here today, Dr. Tuttle, have you</p>	<p style="text-align: right;">Page 28</p> <p>1 Hill methodology to answer the question that</p> <p>2 the J&amp;J attorneys put to you, the same</p> <p>3 question you just summarized?</p> <p>4 A. As I said, the Hill criteria is</p> <p>5 one of the methodologies that I include in my</p> <p>6 report for assessing the body of science and</p> <p>7 the scientific literature.</p> <p>8 Q. Lawyers are sometimes funny</p> <p>9 about words. I understand that you're</p> <p>10 familiar with the methodology and you cite it</p> <p>11 in your report.</p> <p>12 I wanted to know specifically:</p> <p>13 Did you apply, did you use, did you take the</p> <p>14 body of science that you referenced earlier</p> <p>15 and apply the Bradford Hill methodology to</p> <p>16 arrive at an answer to the question posed by</p> <p>17 the J&amp;J attorneys?</p> <p>18 MR. FROST: Objection.</p> <p>19 A. Well, again, as I said, the</p> <p>20 Hill criteria is one of the methodologies</p> <p>21 that I use in my report in assessing the body</p> <p>22 of science and the scientific literature to</p> <p>23 see what the scientific evidence supports.</p> <p>24 ///</p>
<p style="text-align: right;">Page 27</p> <p>1 ever applied the Bradford Hill methodology or</p> <p>2 a like methodology to the issue of a causal</p> <p>3 relationship for a manufactured retail</p> <p>4 product like talcum powder?</p> <p>5 A. I use the Hill criteria</p> <p>6 throughout my work as a toxicologist.</p> <p>7 Q. Understood.</p> <p>8 A. I can't provide a specific</p> <p>9 example where I've used it for a manufactured</p> <p>10 product. I use it regularly in assessing the</p> <p>11 scientific literature in the body of science.</p> <p>12 Q. In this instance, you have used</p> <p>13 the Hill methodology in part to answer the</p> <p>14 question that you described for me earlier,</p> <p>15 that is, the question that the J&amp;J attorneys</p> <p>16 posed to you following your retention. Fair?</p> <p>17 A. As I said, the attorneys asked</p> <p>18 me to assess the body of science and look at</p> <p>19 the scientific evidence regarding a causal</p> <p>20 association between talcum powder and ovarian</p> <p>21 cancer, for which the Hill criteria is one of</p> <p>22 the methodologies that I used in my report</p> <p>23 and discuss in my report.</p> <p>24 Q. Yes, Doctor. Did you use the</p>	<p style="text-align: right;">Page 29</p> <p>1 BY MR. SOILEAU:</p> <p>2 Q. You say it is one of the</p> <p>3 methodologies that you use in your report.</p> <p>4 For what purpose did you use it in your</p> <p>5 report and in connection with your work in</p> <p>6 this matter? Let's approach it from that</p> <p>7 angle.</p> <p>8 MR. FROST: Objection.</p> <p>9 A. Again, I used it to assess the</p> <p>10 body of science and the scientific evidence</p> <p>11 regarding whether the scientific evidence</p> <p>12 supported a causal association between talcum</p> <p>13 powder exposure perineally and ovarian</p> <p>14 cancer.</p> <p>15 BY MR. SOILEAU:</p> <p>16 Q. So you used the Hill</p> <p>17 methodology to determine whether the</p> <p>18 scientific evidence supported a causal</p> <p>19 relationship or association between talcum</p> <p>20 powder exposure and ovarian cancer?</p> <p>21 MR. FROST: Objection.</p> <p>22 BY MR. SOILEAU:</p> <p>23 Q. Is that correct?</p> <p>24 A. As I said the Hill criteria is</p>

8 (Pages 26 to 29)



<p style="text-align: right;">Page 30</p> <p>1 one of the methodologies I discuss and use in 2 my report. 3 Q. I still don't know what you 4 used it for. Can you help me? 5 A. Sure. 6 MR. FROST: Objection. 7 A. I used it to assess the body of 8 science and the scientific evidence to 9 determine whether the scientific -- what the 10 scientific evidence supports regarding the 11 potential for perineal talcum powder exposure 12 to be causally associated with ovarian 13 cancer. 14 BY MR. SOILEAU: 15 Q. And in this case, when we talk 16 about talcum powder exposure, what products 17 are we talking about? 18 A. Again, when we talked a little 19 bit about this previously, in regards to 20 perineal talcum powder exposure, we're 21 dealing with cosmetic talc products. Brands 22 and manufacturers in some of the scientific 23 literature are not specified, so I can't 24 speak to that.</p>	<p style="text-align: right;">Page 32</p> <p>1 regarding perineal talcum powder exposure. 2 And in those studies and studies that I cite, 3 they do not specify a manufacturer or 4 product. 5 Other places in my report, 6 there is research specific to Johnson &amp; 7 Johnson that is addressed and discussed in my 8 report. 9 BY MR. SOILEAU: 10 Q. Do you know what products are 11 at issue in this case? 12 A. It is my understanding that the 13 Johnson &amp; Johnson baby powder and 14 Shower to Shower products are involved in 15 this litigation. 16 Q. How were you first contacted to 17 work in this litigation on behalf of 18 Johnson &amp; Johnson? 19 A. I was first contacted in 20 November of last year, either by Mr. Frost or 21 Ms. Jessica Miller. I can't remember exactly 22 who. 23 Q. Very good. 24 Had you had any prior work or</p>
<p style="text-align: right;">Page 31</p> <p>1 As I mentioned earlier, there 2 is some testing specific to Johnson &amp; 3 Johnson, which is the product specifically 4 involved today, but it is my -- generally 5 speaking, I'm referring to cosmetic talcum 6 powder products. 7 Q. I really want to understand 8 whether a part of your focus and the work 9 that you did in this project was on specific 10 products, talcum powder products, sold by 11 Johnson &amp; Johnson. Was it? 12 MR. FROST: Objection. 13 A. I'm sorry, can you clarify that 14 question for me a little, please? 15 BY MR. SOILEAU: 16 Q. Sure. I wanted to know whether 17 in this project you had a specific focus on 18 particular products sold by Johnson &amp; 19 Johnson, specific talcum powder products sold 20 by Johnson &amp; Johnson? 21 MR. FROST: Objection. 22 A. So in regards to the body of 23 science, as I said, we -- I assessed the 24 scientific evidence and the body of science</p>	<p style="text-align: right;">Page 33</p> <p>1 relationship with Johnson &amp; Johnson before 2 that contact in -- I think you said November 3 of 2018? 4 A. I think I had met them via 5 e-mail in maybe the month prior, but no. 6 Q. The e-mail that you're 7 referring to during the month of October of 8 2018, that e-mail was related to your 9 retention ultimately in this project? 10 A. Yes. 11 Q. So no other work that you have 12 done for Johnson &amp; Johnson in your 13 professional career, regardless of whether it 14 pertained to talcum powder products or some 15 other issue? 16 A. I have not done any work for 17 Johnson &amp; Johnson previously. 18 Q. Okay. Do you know Dr. Nadia 19 Moore? 20 A. I am familiar with Dr. Moore's 21 name. I do not know her personally. 22 Q. Do you only know her name 23 through this litigation? 24 A. I believe so.</p>

Kelly Tuttle, Ph.D.

Page 34	Page 36
<p>1 Q. Did you review her deposition?</p> <p>2 A. Yes, I reviewed her deposition.</p> <p>3 Q. What is her area of expertise?</p> <p>4 A. She's a toxicologist.</p> <p>5 Q. Do you know whether CTEH has</p> <p>6 provided any services to Johnson &amp; Johnson</p> <p>7 other than the project that brings you and I</p> <p>8 together here today?</p> <p>9 A. Not that I'm aware of.</p> <p>10 Q. When you were first retained by</p> <p>11 the attorneys for Johnson &amp; Johnson, what</p> <p>12 familiarity or knowledge did you have about</p> <p>13 the company Johnson &amp; Johnson?</p> <p>14 A. I know the name Johnson &amp;</p> <p>15 Johnson. I use their products personally.</p> <p>16 Beyond that, I don't know that I had any</p> <p>17 knowledge. I had done some personal research</p> <p>18 previously about talcum powder in regards to</p> <p>19 what I'd seen in the news, but beyond that,</p> <p>20 nothing specific.</p> <p>21 Q. Very good.</p> <p>22 Nothing really that was aimed</p> <p>23 at the company Johnson &amp; Johnson, only at</p> <p>24 talcum powder and some talcum powder</p>	<p>1 broad question because Johnson &amp; Johnson</p> <p>2 manufactures lots of products, right?</p> <p>3 A. Yes.</p> <p>4 Q. I meant to include, but I</p> <p>5 admittedly did not, what talcum powder</p> <p>6 products manufactured by Johnson &amp; Johnson</p> <p>7 have you used in the past?</p> <p>8 A. I have talcum powder, the baby</p> <p>9 powder, for my son.</p> <p>10 Q. You're the mother of a newborn?</p> <p>11 A. Yes.</p> <p>12 Q. And it's your first child?</p> <p>13 A. It is.</p> <p>14 Q. And you use Johnson &amp; Johnson's</p> <p>15 baby powder on your newborn baby?</p> <p>16 A. Yes, I do.</p> <p>17 Q. And do you use the talcum</p> <p>18 powder?</p> <p>19 A. I do.</p> <p>20 Q. Okay. Had you previously used</p> <p>21 any Johnson &amp; Johnson talcum powder products?</p> <p>22 A. Again, I would have to go back</p> <p>23 and look specifically. I haven't looked at</p> <p>24 the ingredients in all the products that I</p>
Page 35	Page 37
<p>1 products, fair?</p> <p>2 A. I'm sorry, what do you mean,</p> <p>3 the...</p> <p>4 Q. I asked you if you had any</p> <p>5 familiarity, and I think what you told me</p> <p>6 basically, and I just wanted to make sure I</p> <p>7 understood, that you really didn't have any</p> <p>8 specific familiarity with the company,</p> <p>9 although you had looked at the products and</p> <p>10 had some familiarity with particular</p> <p>11 products, talcum powder products, fair?</p> <p>12 A. As I said, I know the name</p> <p>13 Johnson &amp; Johnson. I use their products, and</p> <p>14 I had seen some of the news articles in</p> <p>15 previous years regarding Johnson &amp; Johnson.</p> <p>16 Q. Okay. Which products</p> <p>17 manufactured by Johnson &amp; Johnson have you</p> <p>18 used, Doctor?</p> <p>19 A. Oh. I would have to go through</p> <p>20 my bathroom and see what all products are</p> <p>21 there, but I --</p> <p>22 Q. That's fair. Let me interrupt</p> <p>23 and narrow my question. I don't want to</p> <p>24 interrupt you today, but I realize that was a</p>	<p>1 use in my bathroom, so I'm not sure.</p> <p>2 Q. Well, have you used</p> <p>3 Shower to Shower?</p> <p>4 A. No, I haven't.</p> <p>5 Q. Have you used any like talcum</p> <p>6 powder product, and I just mean a talcum</p> <p>7 powder product that's used for personal use?</p> <p>8 A. Again, I would have to look at</p> <p>9 the ingredients of the products that I have</p> <p>10 in my bathroom. I don't know the specific</p> <p>11 ingredients for everything that's in my</p> <p>12 bathroom.</p> <p>13 Q. When did you do the personal</p> <p>14 research that you referenced a few moments</p> <p>15 ago?</p> <p>16 A. A few years ago when I had seen</p> <p>17 some news articles coming out, I just briefly</p> <p>18 on my own time got into the scientific</p> <p>19 literature and kind of looked at the issue</p> <p>20 that was being discussed.</p> <p>21 Q. Were you working for CTEH at</p> <p>22 that time?</p> <p>23 A. I believe so, yes.</p> <p>24 Q. Were you married?</p>

10 (Pages 34 to 37)

Kelly Tuttle, Ph.D.

<p style="text-align: right;">Page 38</p> <p>1 A. I don't think so, no.</p> <p>2 Q. Okay. And I don't -- perhaps</p> <p>3 it's apparent, but I don't think you know</p> <p>4 exactly when you did this research. Maybe I</p> <p>5 should have asked.</p> <p>6 Do you know exactly when you</p> <p>7 began to conduct this personal research?</p> <p>8 A. Not exactly, no.</p> <p>9 Q. Is it fair to say that your</p> <p>10 best estimate would be sometime after you</p> <p>11 went to work with CTEH but before you were</p> <p>12 married?</p> <p>13 A. Yes, I believe so.</p> <p>14 Q. Are there any other events that</p> <p>15 would help us pin it down more specifically?</p> <p>16 A. No, not specifically. It's a</p> <p>17 common practice of mine, so I don't know that</p> <p>18 I could really specify when I particularly</p> <p>19 researched it.</p> <p>20 Q. What steps did you undertake,</p> <p>21 Doctor, when you conducted this personal</p> <p>22 research into talcum powder products?</p> <p>23 A. It was just a very general</p> <p>24 cursory dive into the scientific literature,</p>	<p style="text-align: right;">Page 40</p> <p>1 November of last year?</p> <p>2 A. I don't know that there was</p> <p>3 necessarily a conclusion. As I said, I saw</p> <p>4 it. It triggered my interest. I looked into</p> <p>5 the scientific literature. You know, it</p> <p>6 certainly wasn't something that I was doing</p> <p>7 formally or with any particular endpoint in</p> <p>8 mind. It was more of just a general</p> <p>9 examination.</p> <p>10 Q. Did you print any articles that</p> <p>11 you discovered through your PubMed or other</p> <p>12 personal research?</p> <p>13 A. I don't think I did, no.</p> <p>14 Q. Did you at some point weigh the</p> <p>15 evidence that you had seen in order to</p> <p>16 research a conclusion on the safety of talcum</p> <p>17 powder products?</p> <p>18 MR. FROST: Objection.</p> <p>19 A. As I said, it wasn't a formal</p> <p>20 assessment. There wasn't really a</p> <p>21 conclusion. It was a general look at the</p> <p>22 body of science to see what the body of</p> <p>23 science said on the matter.</p> <p>24 ///</p>
<p style="text-align: right;">Page 39</p> <p>1 some PubMed searches, some Google Scholar</p> <p>2 searches, just looking at the body of</p> <p>3 science.</p> <p>4 Q. You say cursory dive, but a</p> <p>5 cursory dive as a toxicologist, right?</p> <p>6 A. Yes.</p> <p>7 Q. So you did look into PubMed and</p> <p>8 Google Scholar, you said?</p> <p>9 A. Yes.</p> <p>10 Q. Okay. And did you make notes?</p> <p>11 A. No, I didn't make any notes.</p> <p>12 Q. Did you do anything to -- well,</p> <p>13 strike that.</p> <p>14 How long did you continue to</p> <p>15 conduct this personal research?</p> <p>16 A. I don't know how long I spent</p> <p>17 doing it. As I said, it was just a matter of</p> <p>18 personal interest. It's a common practice of</p> <p>19 mine to try to, you know, read the literature</p> <p>20 on a regular basis, so I don't know how long</p> <p>21 I spent.</p> <p>22 Q. Did you conclude this personal</p> <p>23 research at some point prior to the time that</p> <p>24 you were contacted in October of -- or</p>	<p style="text-align: right;">Page 41</p> <p>1 BY MR. SOILEAU:</p> <p>2 Q. For what purpose?</p> <p>3 A. For personal interest.</p> <p>4 Q. Well, was it simple curiosity,</p> <p>5 or were you also interested in the safety of</p> <p>6 the talcum powder products?</p> <p>7 A. Well, again, it is curiosity.</p> <p>8 As a toxicologist, I have just a general</p> <p>9 interest in toxicological matters and</p> <p>10 toxicological research, and I certainly --</p> <p>11 whenever I see things in media or other</p> <p>12 sources, I like to see what the scientific</p> <p>13 basis is for the statements that are being</p> <p>14 made to see if the science supports it or</p> <p>15 doesn't support it.</p> <p>16 Q. And what conclusion did you</p> <p>17 reach?</p> <p>18 MR. FROST: Objection.</p> <p>19 A. Again, you know, there wasn't</p> <p>20 really an end goal of making a conclusion.</p> <p>21 You know, as I said, when I reviewed the</p> <p>22 scientific literature, I certainly didn't see</p> <p>23 the body of science showing a strong evidence</p> <p>24 to support anything in regards to the</p>

11 (Pages 38 to 41)



Kelly Tuttle, Ph.D.

<p style="text-align: right;">Page 42</p> <p>1 statements that I was -- you know, the</p> <p>2 general nuances that were being put forth in</p> <p>3 the media.</p> <p>4 BY MR. SOILEAU:</p> <p>5 Q. Did you rely on that personal</p> <p>6 research in deciding to use Johnson &amp;</p> <p>7 Johnson's baby powder on your newborn?</p> <p>8 MR. FROST: Objection.</p> <p>9 A. I certainly used my -- you</p> <p>10 know, I certainly looked at the scientific</p> <p>11 knowledge and the body of science in regards</p> <p>12 to using Johnson &amp; Johnson baby powder on my</p> <p>13 newborn. I mean, I knew the literature</p> <p>14 before I had my son.</p> <p>15 BY MR. SOILEAU:</p> <p>16 Q. What had you heard through news</p> <p>17 articles that triggered this personal</p> <p>18 research?</p> <p>19 A. Goodness, it was so many years</p> <p>20 ago. I remember seeing something about a</p> <p>21 large case that had just come to an end</p> <p>22 regarding talcum powder and ovarian cancer.</p> <p>23 Q. Did you reach an opinion based</p> <p>24 on your personal research that the use of</p>	<p style="text-align: right;">Page 44</p> <p>1 A. Yes.</p> <p>2 Q. Those did not come from</p> <p>3 scientists, did they?</p> <p>4 A. I don't remember at this point</p> <p>5 who was making the statements, but they were</p> <p>6 in the general media.</p> <p>7 Q. Okay. Certainly they did not</p> <p>8 appear in scientific literature, fair?</p> <p>9 A. The ones that piqued my</p> <p>10 interest were -- I don't believe -- no, I</p> <p>11 don't believe they were in the scientific</p> <p>12 literature.</p> <p>13 Q. So then you turned as a</p> <p>14 toxicologist to the scientific literature to</p> <p>15 conduct this personal research in response to</p> <p>16 the media reports, correct?</p> <p>17 MR. FROST: Objection.</p> <p>18 A. As I said, not necessarily in</p> <p>19 response. The media reports piqued my</p> <p>20 interest, and so I looked at the body of</p> <p>21 science regarding it.</p> <p>22 BY MR. SOILEAU:</p> <p>23 Q. All right. You had not looked</p> <p>24 at the body of science regarding talcum</p>
<p style="text-align: right;">Page 43</p> <p>1 talcum powder products was safe?</p> <p>2 MR. FROST: Objection.</p> <p>3 A. Well, again, at the time, I was</p> <p>4 doing it more for personal interest as</p> <p>5 opposed to any general conclusions, but as I</p> <p>6 said, my impression at the time was that the</p> <p>7 scientific evidence did not support the</p> <p>8 statements being made in the media.</p> <p>9 BY MR. SOILEAU:</p> <p>10 Q. But did you determine that the</p> <p>11 use of talcum powder products based on your</p> <p>12 own personal research was safe?</p> <p>13 MR. FROST: Objection.</p> <p>14 A. Again, that wasn't the specific</p> <p>15 end goal. There wasn't a specific end goal</p> <p>16 in my assessment of the scientific</p> <p>17 literature. I had seen the media statements</p> <p>18 that had piqued my interest. I did a general</p> <p>19 look into the body of science to see if the</p> <p>20 body of science supported the statements</p> <p>21 being made by the media.</p> <p>22 BY MR. SOILEAU:</p> <p>23 Q. So you heard some statements or</p> <p>24 read some statements in the media, fair?</p>	<p style="text-align: right;">Page 45</p> <p>1 powder products before you came into contact</p> <p>2 with these media reports; is that correct?</p> <p>3 A. Not that I recall.</p> <p>4 Q. Okay. So you became aware of</p> <p>5 the media reports, and then that piqued your</p> <p>6 interest and you turned to the scientific</p> <p>7 literature?</p> <p>8 A. Regarding the role of talcum</p> <p>9 powder in ovarian cancer, yes.</p> <p>10 Q. Okay. And when you turned to</p> <p>11 the literature, you turned to the scientific</p> <p>12 literature, correct?</p> <p>13 A. That's correct.</p> <p>14 Q. And when you looked at the</p> <p>15 scientific literature, you looked at that</p> <p>16 literature as a toxicologist, right?</p> <p>17 MR. FROST: Objection.</p> <p>18 A. I applied my -- excuse me --</p> <p>19 training and expertise as a toxicologist in</p> <p>20 reading the literature. I don't know what it</p> <p>21 means to look at it as a tox- -- as a</p> <p>22 toxicologist.</p> <p>23 BY MR. SOILEAU:</p> <p>24 Q. Well, the Casarett exhibit we</p>

Kelly Tuttle, Ph.D.

<p style="text-align: right;">Page 46</p> <p>1 looked at before said that toxicology offers</p> <p>2 a way to understand, prevent, mitigate and</p> <p>3 treat the potentially harmful consequences of</p> <p>4 substances.</p> <p>5 Do you recall that? You have</p> <p>6 it there.</p> <p>7 A. Yes, I recall us discussing it,</p> <p>8 yes.</p> <p>9 Q. I mean, isn't that what you</p> <p>10 were doing, looking at scientific literature</p> <p>11 to understand and potentially prevent any</p> <p>12 potentially harmful consequences of this</p> <p>13 particular product, talcum powder?</p> <p>14 MR. FROST: Objection.</p> <p>15 A. As I said, I was looking at the</p> <p>16 scientific literature to see whether the</p> <p>17 scientific evidence was supportive of what</p> <p>18 had been -- what I had read or seen in the</p> <p>19 media at the time.</p> <p>20 BY MR. SOILEAU:</p> <p>21 Q. Okay. Do you know as we sit</p> <p>22 here today whether Johnson &amp; Johnson employs</p> <p>23 toxicologists?</p> <p>24 A. I don't know who Johnson &amp;</p>	<p style="text-align: right;">Page 48</p> <p>1 really just asking about your expectation,</p> <p>2 and if you don't know and you don't have one,</p> <p>3 you can certainly tell me that.</p> <p>4 But would you have, based on</p> <p>5 your education, experience and background,</p> <p>6 any expectation whether a company like</p> <p>7 Johnson &amp; Johnson would employ scientists,</p> <p>8 including toxicologists, to look at any</p> <p>9 hazards that may be included within their</p> <p>10 products?</p> <p>11 MR. FROST: Objection.</p> <p>12 A. I'm sorry. That...</p> <p>13 BY MR. SOILEAU:</p> <p>14 Q. Too long?</p> <p>15 A. Yes.</p> <p>16 Q. All right. You have education,</p> <p>17 experience, training and other background in</p> <p>18 the area of toxicology, right?</p> <p>19 A. Yes, that's correct.</p> <p>20 Q. And we've talked a little bit</p> <p>21 about what toxicology is. I'm simply asking</p> <p>22 you as a professional: Would you expect that</p> <p>23 a company like Johnson &amp; Johnson that sells</p> <p>24 talcum powder products among its product</p>
<p style="text-align: right;">Page 47</p> <p>1 Johnson employs.</p> <p>2 Q. Well, of course, to be clear,</p> <p>3 you understand I'm not asking you for the</p> <p>4 names of particular toxicologists, right?</p> <p>5 A. Yes, I understand.</p> <p>6 Q. Okay. But do you have any -- a</p> <p>7 sense of whether they have their own</p> <p>8 scientists on staff, including toxicologists?</p> <p>9 MR. FROST: Objection.</p> <p>10 A. Again, I don't know who</p> <p>11 Johnson &amp; Johnson specifically employs on</p> <p>12 their staff.</p> <p>13 BY MR. SOILEAU:</p> <p>14 Q. Would you expect that Johnson &amp;</p> <p>15 Johnson would have, as part of its team,</p> <p>16 scientists, including toxicologists with</p> <p>17 training and background similar to yours?</p> <p>18 MR. FROST: Objection.</p> <p>19 A. Again, I don't know who</p> <p>20 Johnson &amp; Johnson hires or directly employs,</p> <p>21 so I can't speak to what their training and</p> <p>22 experience would be.</p> <p>23 BY MR. SOILEAU:</p> <p>24 Q. I understand that, Doctor. I'm</p>	<p style="text-align: right;">Page 49</p> <p>1 lines would have, within its company,</p> <p>2 scientists, including scientists with a</p> <p>3 background similar to yours, to assess any</p> <p>4 hazard their products might present?</p> <p>5 MR. FROST: Objection.</p> <p>6 A. And again, I don't know who</p> <p>7 Johnson &amp; Johnson hires directly or how they</p> <p>8 do their manufacturing process or testing</p> <p>9 processes.</p> <p>10 BY MR. SOILEAU:</p> <p>11 Q. From your perspective, do you</p> <p>12 have any expertise in the regulatory area?</p> <p>13 A. So in regards to my training</p> <p>14 and expertise in toxicology, that involves a</p> <p>15 wide range of subcategories, including</p> <p>16 regulatory aspects of toxicology and</p> <p>17 regulations regarding toxicological aspects.</p> <p>18 Q. Okay. Let me show you an</p> <p>19 additional exhibit.</p> <p>20 (Comments off the stenographic</p> <p>21 record.)</p> <p>22 MR. SOILEAU: I'm sorry,</p> <p>23 Doctor, I have a -- here we go. I</p> <p>24 have a natural ability to lose items,</p>

13 (Pages 46 to 49)

Kelly Tuttle, Ph.D.

Page 50	Page 52
<p>1 and I lost our exhibit stickers for a</p> <p>2 moment, but I have found them.</p> <p>3 (Whereupon, Deposition Exhibit</p> <p>4 Tuttle-6, 21 C.F.R. 740, was marked</p> <p>5 for identification.)</p> <p>6 BY MR. SOILEAU:</p> <p>7 Q. Let me show you a document I'll</p> <p>8 mark as Tuttle Exhibit 6. It's a two-page</p> <p>9 document. And I just want to know if this is</p> <p>10 something that, first, is familiar to you.</p> <p>11 And not necessarily the</p> <p>12 document, Doctor, but to be specific, this</p> <p>13 document shows a copy of a regulation from</p> <p>14 the Code of Federal Regulations Title 21,</p> <p>15 740, Section 740.1.</p> <p>16 Are you familiar with this</p> <p>17 section from the Code of Federal Regulations?</p> <p>18 A. I would need to look at it.</p> <p>19 Looks like it's a very brief paragraph. I'm</p> <p>20 familiar with the Code of Federal Regulations</p> <p>21 and the general documents.</p> <p>22 Q. Well, let me ask you this:</p> <p>23 This document says, and specifically subpart</p> <p>24 (a) of Section 740.1 says that the label of a</p>	<p>1 BY MR. SOILEAU:</p> <p>2 Q. Well, could you agree that good</p> <p>3 practices of a company include an obligation</p> <p>4 to identify hazards that may be associated</p> <p>5 with the products that it presents for sale</p> <p>6 to citizen consumers?</p> <p>7 A. Well, again --</p> <p>8 MR. FROST: Objection.</p> <p>9 A. -- that's a very broad</p> <p>10 statement. It depends. You have to look at</p> <p>11 specifics, specifically what questions you're</p> <p>12 wanting to answer, what the regulations say</p> <p>13 regarding individual products and assessments</p> <p>14 and things. So, you know, that's overly</p> <p>15 broad to just say yes or no.</p> <p>16 BY MR. SOILEAU:</p> <p>17 Q. Okay. One of the things I want</p> <p>18 to understand today as we talk is the scope</p> <p>19 of your expertise and the issues or topics</p> <p>20 that you might address through your</p> <p>21 testimony, and I know you told me that you</p> <p>22 have some contact with regulatory matters.</p> <p>23 I'm really not asking you to</p> <p>24 interpret or list regulations right now. I'm</p>
Page 51	Page 53
<p>1 cosmetic product shall bear a warning</p> <p>2 statement whenever necessary or appropriate</p> <p>3 to prevent a health hazard that may be</p> <p>4 associated with the product.</p> <p>5 Do you agree with that?</p> <p>6 MR. FROST: Objection to form.</p> <p>7 A. Well, this is one subpart of</p> <p>8 the entire part 740 that was -- was not</p> <p>9 provided for review to put the additional</p> <p>10 context for this, so I can't -- without</p> <p>11 knowing more or being able to read the entire</p> <p>12 regulations regarding this for context, I</p> <p>13 can't agree or disagree.</p> <p>14 BY MR. SOILEAU:</p> <p>15 Q. Okay. Very well.</p> <p>16 Let me ask you this: As a</p> <p>17 toxicologist with your training and</p> <p>18 background and the experience that you bring</p> <p>19 to this project, do you believe that a</p> <p>20 manufacturer has an obligation to identify</p> <p>21 hazards that may be associated with its</p> <p>22 products?</p> <p>23 MR. FROST: Objection.</p> <p>24 A. It depends.</p>	<p>1 just asking you as a toxicologist with your</p> <p>2 training and background, do you have an</p> <p>3 understanding about good practices for a</p> <p>4 company like Johnson &amp; Johnson?</p> <p>5 MR. FROST: Objection.</p> <p>6 A. Well, as I said, as part of my</p> <p>7 training and experience in working in</p> <p>8 toxicology, I work with regulatory guidelines</p> <p>9 and regulatory standards. You know, I can't</p> <p>10 speak to what good practices would be. You</p> <p>11 know, that's kind of a general term.</p> <p>12 As I said, I spend a lot of</p> <p>13 time reading regulations and looking at</p> <p>14 regulations, but regarding good practices for</p> <p>15 a company or anything like that, I would need</p> <p>16 to look at the regulations.</p> <p>17 BY MR. SOILEAU:</p> <p>18 Q. Do you ever work directly with</p> <p>19 companies, companies like Johnson &amp; Johnson,</p> <p>20 who present for sale to citizen consumers</p> <p>21 products like talcum powder products that are</p> <p>22 at issue in this case?</p> <p>23 MR. FROST: Objection.</p> <p>24 A. I have worked with companies in</p>

14 (Pages 50 to 53)

Kelly Tuttle, Ph.D.

<p style="text-align: right;">Page 54</p> <p>1 regards to product information and product --</p> <p>2 and regulations regarding products. I don't</p> <p>3 think that I've been involved with any that</p> <p>4 were direct-to-consumer products.</p> <p>5 BY MR. SOILEAU:</p> <p>6 Q. What about warning? Have you</p> <p>7 ever worked on a warning? For example, a</p> <p>8 company brings you some item that may be a</p> <p>9 retail product, it may be used in industry,</p> <p>10 asked you to assist that company in preparing</p> <p>11 an appropriate warning associated with the</p> <p>12 product.</p> <p>13 Ever done that?</p> <p>14 A. So I've worked with companies</p> <p>15 in the generation of material safety data</p> <p>16 sheets under the Global Harmonization</p> <p>17 Standard as well as any warnings or labels</p> <p>18 required by the Global Harmonization</p> <p>19 Standard.</p> <p>20 Q. What companies have you worked</p> <p>21 with on the issue of warnings?</p> <p>22 MR. FROST: Objection to the</p> <p>23 extent it's not confidential.</p> <p>24 A. I'm trying to --</p>	<p style="text-align: right;">Page 56</p> <p>1 for a product is to identify from the</p> <p>2 perspective of a toxicologist any potential</p> <p>3 hazard the product might present?</p> <p>4 A. So that's a little broad. In</p> <p>5 regards to hazards and labeling, the Global</p> <p>6 Harmonization Standard puts forth some</p> <p>7 guidelines regarding that, but you assess the</p> <p>8 body of science, the scientific literature</p> <p>9 and the information available. It would,</p> <p>10 again, depend on the product, what was being</p> <p>11 manufactured, what we were looking at, what</p> <p>12 was the question.</p> <p>13 Q. You say in part it would depend</p> <p>14 on the product. I mean, from a fundamental</p> <p>15 level, I mean, isn't it true that you need to</p> <p>16 know if there are any hazards presented by a</p> <p>17 product before you consider what, if any,</p> <p>18 warnings are appropriate or necessary?</p> <p>19 A. Well, it's not just quite as</p> <p>20 simple as that. Like I said, you have to</p> <p>21 look at the scientific literature regarding</p> <p>22 what the science shows. There's some</p> <p>23 guidelines set forth in the Global</p> <p>24 Harmonization Standard regarding how hazard</p>
<p style="text-align: right;">Page 55</p> <p>1 BY MR. SOILEAU:</p> <p>2 Q. Yeah. Go ahead. If there's</p> <p>3 some issue of confidentiality, I'm not asking</p> <p>4 about the product, the warning or any of the</p> <p>5 product data that you might have reviewed.</p> <p>6 I'm just asking you: What</p> <p>7 companies have you provided input on warnings</p> <p>8 to?</p> <p>9 A. I don't know that I can recall</p> <p>10 all of them. As you said, I don't know if</p> <p>11 there's anything regarding confidentiality.</p> <p>12 I have done some work with Nucor Steel</p> <p>13 previously.</p> <p>14 Q. Well, can we agree that an</p> <p>15 initial step is to determine whether any</p> <p>16 hazard exists in the particular product or</p> <p>17 item that you are looking at and considering?</p> <p>18 Did that question make sense to</p> <p>19 you?</p> <p>20 A. Could you clarify it for me,</p> <p>21 please?</p> <p>22 Q. Sure.</p> <p>23 Can we agree that an initial</p> <p>24 step in determining an appropriate warning</p>	<p style="text-align: right;">Page 57</p> <p>1 statements and labels are used based on the</p> <p>2 body of science and the scientific evidence.</p> <p>3 Q. Have you at any time, in this</p> <p>4 project or otherwise, taken any steps or</p> <p>5 undertaken any work as a toxicologist to</p> <p>6 identify any hazards associated with talcum</p> <p>7 powder products?</p> <p>8 MR. FROST: Objection.</p> <p>9 A. Well, as I said in this</p> <p>10 particular case, I was asked to assess the</p> <p>11 body of science regarding a -- whether the</p> <p>12 body of science supports the evidence for a</p> <p>13 causal association between talcum powder</p> <p>14 applied perineally and ovarian cancer.</p> <p>15 BY MR. SOILEAU:</p> <p>16 Q. Do you recognize the words</p> <p>17 "hazard assessment"?</p> <p>18 A. Yes.</p> <p>19 Q. What do those words mean to you</p> <p>20 as a toxicologist?</p> <p>21 A. Well, I don't know that I have</p> <p>22 a personal view. They are defined in various</p> <p>23 regulations and guidelines. I don't know</p> <p>24 that I personally have a definition. I would</p>

15 (Pages 54 to 57)

Kelly Tuttle, Ph.D.

<p style="text-align: right;">Page 58</p> <p>1 refer to those for a specific definition.</p> <p>2 Q. Is hazard assessment something</p> <p>3 that you as a toxicologist have been trained</p> <p>4 to perform?</p> <p>5 A. Yes, I have performed hazard</p> <p>6 assessments.</p> <p>7 Q. Is there a methodology that you</p> <p>8 are familiar with that is used for the</p> <p>9 performance of hazard assessments?</p> <p>10 A. I believe I touched on that</p> <p>11 briefly in my report, though not in depth.</p> <p>12 It would depend. There are some guidelines</p> <p>13 in the regulatory agencies in regards to</p> <p>14 hazard assessment.</p> <p>15 Q. There's one than more -- I'm</p> <p>16 sorry, I tangled that up. I apologize.</p> <p>17 There's more than one</p> <p>18 methodology out there can be used</p> <p>19 appropriately by toxicologists to conduct a</p> <p>20 hazard assessment, correct?</p> <p>21 MR. FROST: Objection.</p> <p>22 A. I would have to look at the</p> <p>23 methodologies in question. I'd have to look</p> <p>24 at the guidelines to see what methodologies</p>	<p style="text-align: right;">Page 60</p> <p>1 MR. FROST: Objection.</p> <p>2 A. Well, again, regarding risk</p> <p>3 assessment, I would need to look at the</p> <p>4 methodologies you're discussing specifically</p> <p>5 so I could actually refer to them. You</p> <p>6 referred to multiple methodologies. I would</p> <p>7 need to see them to be able to compare them</p> <p>8 and see what the guidelines and regulations</p> <p>9 say.</p> <p>10 BY MR. SOILEAU:</p> <p>11 Q. Right. But I'm not asking you</p> <p>12 now about all of the methodologies. I was</p> <p>13 just asking you if you recognized the NRC</p> <p>14 risk assessment methodology as one of the</p> <p>15 methodologies that a toxicologist might use</p> <p>16 to perform an assessment?</p> <p>17 A. And as I said, I'd need to see</p> <p>18 the methodology to be able to answer that</p> <p>19 appropriately.</p> <p>20 Q. Okay. As we sit here today,</p> <p>21 you would not have an criticism of the use</p> <p>22 of the NRC risk assessment methodology for</p> <p>23 risk or hazard assessment, would you?</p> <p>24 MR. FROST: Objection.</p>
<p style="text-align: right;">Page 59</p> <p>1 you're discussing, if there are differences</p> <p>2 in them or anything else.</p> <p>3 BY MR. SOILEAU:</p> <p>4 Q. Okay. Very well.</p> <p>5 Doctor, is there, however, a</p> <p>6 particular methodology that you use and</p> <p>7 employ and consider appropriate for hazard</p> <p>8 assessment?</p> <p>9 A. Well, as I said, it would</p> <p>10 depend. I'd have to go look at the</p> <p>11 regulations to see what is put forth in those</p> <p>12 regulations regarding the methodologies for</p> <p>13 hazard assessment. I can't just speak to it</p> <p>14 generally.</p> <p>15 Q. Okay. Have you ever performed</p> <p>16 a hazard assessment?</p> <p>17 A. It's been a while, but yes.</p> <p>18 Q. Okay. Are you familiar with</p> <p>19 the NRC risk assessment methodology?</p> <p>20 A. Vaguely, yes.</p> <p>21 Q. Is it generally accepted from</p> <p>22 your perspective as a toxicologist as one of</p> <p>23 the methodologies that might be used for</p> <p>24 hazard or risk assessment by a toxicologist?</p>	<p style="text-align: right;">Page 61</p> <p>1 A. Again, without having the</p> <p>2 methodology in front of me so I could look at</p> <p>3 it specifically, I couldn't say one way or</p> <p>4 the other.</p> <p>5 BY MR. SOILEAU:</p> <p>6 Q. Fair enough.</p> <p>7 Did you make any -- well, let's</p> <p>8 ask this first.</p> <p>9 Did you have any conversations,</p> <p>10 any discussions with any representatives of</p> <p>11 Johnson &amp; Johnson, other than the attorneys</p> <p>12 retained to defend Johnson &amp; Johnson? Any</p> <p>13 representatives of Johnson &amp; Johnson other</p> <p>14 than their retained defense attorneys?</p> <p>15 A. No, I have not.</p> <p>16 Q. Did you take any steps to find</p> <p>17 out if the folks at Johnson &amp; Johnson thought</p> <p>18 that their talcum powder products were safe?</p> <p>19 MR. FROST: Objection.</p> <p>20 A. No, I did not.</p> <p>21 BY MR. SOILEAU:</p> <p>22 Q. Have you assumed in your work</p> <p>23 during this case that the folks at Johnson &amp;</p> <p>24 Johnson believed that their talcum powder</p>



Kelly Tuttle, Ph.D.

<p style="text-align: right;">Page 62</p> <p>1 products are safe?</p> <p>2 MR. FROST: Objection.</p> <p>3 A. I was not asked to look at what</p> <p>4 Johnson &amp; Johnson thought. I was asked to</p> <p>5 examine the body of science and the</p> <p>6 scientific evidence.</p> <p>7 BY MR. SOILEAU:</p> <p>8 Q. Can you -- strike that.</p> <p>9 Wouldn't you expect that</p> <p>10 Johnson &amp; Johnson would have its own body of</p> <p>11 scientific evidence and scientific</p> <p>12 information addressing talcum powder</p> <p>13 products?</p> <p>14 MR. FROST: Objection.</p> <p>15 BY MR. SOILEAU:</p> <p>16 Q. Its talcum powder products?</p> <p>17 A. Again, I was asked to assess</p> <p>18 the scientific literature and the body of</p> <p>19 evidence regarding a -- whether the evidence</p> <p>20 supported a causal association between</p> <p>21 perineal talcum powder application and</p> <p>22 ovarian cancer.</p> <p>23 It wouldn't really -- what</p> <p>24 Johnson &amp; Johnson thought or anything</p>	<p style="text-align: right;">Page 64</p> <p>1 that be fair, to say that you intended to</p> <p>2 look at the entire available body of science</p> <p>3 as a whole?</p> <p>4 MR. FROST: Objection.</p> <p>5 A. Well, the entire body of</p> <p>6 science can -- you know, when you're</p> <p>7 searching PubMed and searching Google Scholar</p> <p>8 or looking at these sources, you're sifting</p> <p>9 through thousands to millions of scientific</p> <p>10 articles on a range of topics. So we</p> <p>11 certainly attempt to be comprehensive and</p> <p>12 address the topic as put forth in the</p> <p>13 scientific literature thoroughly.</p> <p>14 But when you're dealing with</p> <p>15 that many publications and that sheer amount</p> <p>16 of data, you know, there's no guarantee that</p> <p>17 you have found literally every applicable</p> <p>18 publication in the scientific literature.</p> <p>19 BY MR. SOILEAU:</p> <p>20 Q. That makes sense.</p> <p>21 Can we agree that in gathering</p> <p>22 the scientific literature, it is your</p> <p>23 intention and you aspire to gather all of the</p> <p>24 relevant scientific information?</p>
<p style="text-align: right;">Page 63</p> <p>1 wouldn't play a role in the assessment of the</p> <p>2 scientific literature.</p> <p>3 Q. Was the scientific literature,</p> <p>4 the body of evidence that you considered, was</p> <p>5 it provided to you, or did you take any steps</p> <p>6 to generate or assimilate that body of</p> <p>7 scientific literature and evidence?</p> <p>8 A. No, the literature was not</p> <p>9 provided to me. I did the literature reviews</p> <p>10 myself as well as -- we have an information</p> <p>11 specialist at CTEH that helps with</p> <p>12 interlibrary loans and PubMed searches and</p> <p>13 things of that nature.</p> <p>14 Q. An information specialist?</p> <p>15 A. Yes.</p> <p>16 Q. Who is that?</p> <p>17 A. Her name is Samantha Nation.</p> <p>18 Q. Was it your intention in</p> <p>19 gathering scientific literature and evidence</p> <p>20 to be thorough and complete?</p> <p>21 A. It was certainly my intent to</p> <p>22 look at the body of science as a whole.</p> <p>23 Q. And when you say as a whole,</p> <p>24 the entire available body of science? Would</p>	<p style="text-align: right;">Page 65</p> <p>1 MR. FROST: Objection.</p> <p>2 A. We certainly attempt to gather</p> <p>3 as much, you know, applicable and, you know,</p> <p>4 the scientific evidence that discusses the</p> <p>5 question we're trying to answer as best we</p> <p>6 can.</p> <p>7 BY MR. SOILEAU:</p> <p>8 Q. But for the reasons you</p> <p>9 outlined a moment ago, it can be hard to find</p> <p>10 studies on a particular question or issue,</p> <p>11 fair?</p> <p>12 A. Well, I said it can certainly</p> <p>13 be hard to say that you have found every</p> <p>14 article that has ever been published on any</p> <p>15 given topic.</p> <p>16 Q. Wouldn't you expect that</p> <p>17 Johnson &amp; Johnson would be an excellent</p> <p>18 source for relevant scientific literature and</p> <p>19 evidence on the question of any relationship</p> <p>20 between perineal application of talcum powder</p> <p>21 products and ovarian cancer?</p> <p>22 MR. FROST: Objection.</p> <p>23 A. I don't know what Johnson &amp;</p> <p>24 Johnson maintains as far as scientific</p>

17 (Pages 62 to 65)

Kelly Tuttle, Ph.D.

<p style="text-align: right;">Page 66</p> <p>1 literature or what they would do as far as</p> <p>2 being a source for that kind of thing. I</p> <p>3 went to my established databases and did the</p> <p>4 searches myself to find the literature.</p> <p>5 BY MR. SOILEAU:</p> <p>6 Q. Do you know how long Johnson &amp;</p> <p>7 Johnson as a company has been marketing to</p> <p>8 the public talcum powder products?</p> <p>9 MR. FROST: Objection.</p> <p>10 A. No, I do not.</p> <p>11 BY MR. SOILEAU:</p> <p>12 Q. Okay. And you said you don't</p> <p>13 know what Johnson &amp; Johnson maintains. Did</p> <p>14 you ask at any point?</p> <p>15 A. No, I did not.</p> <p>16 Q. So as we sit here today, you do</p> <p>17 not know whether Johnson &amp; Johnson believes</p> <p>18 its talcum powder products are safe?</p> <p>19 MR. FROST: Objection.</p> <p>20 A. Well, as I said, I was asked to</p> <p>21 look at the body of science and the</p> <p>22 scientific evidence regarding whether</p> <p>23 perineal talc exposure was causally</p> <p>24 associated with ovarian cancer, regarding --</p>	<p style="text-align: right;">Page 68</p> <p>1 peer-reviewed scientific literature. I do</p> <p>2 not know, as I said, what Johnson &amp; Johnson</p> <p>3 has done or maintained.</p> <p>4 BY MR. SOILEAU:</p> <p>5 Q. Okay. Were you provided with</p> <p>6 Johnson &amp; Johnson documents that might speak</p> <p>7 to any relationship between perineal</p> <p>8 application of talcum powder products and</p> <p>9 ovarian cancer?</p> <p>10 MR. FROST: Objection.</p> <p>11 A. I am not -- as I said, I'm not</p> <p>12 aware of what Johnson &amp; Johnson has. The</p> <p>13 materials that were provided to me are listed</p> <p>14 in my report under the materials reviewed and</p> <p>15 relied upon.</p> <p>16 BY MR. SOILEAU:</p> <p>17 Q. All right. Look at page 2 of</p> <p>18 your report, if you would, Section 3.0.</p> <p>19 Do you have that page, Doctor?</p> <p>20 A. Yes, I do.</p> <p>21 Q. You see that 3.0 has a number</p> <p>22 of bulleted items?</p> <p>23 A. Yes.</p> <p>24 Q. The last one says, quote "Other</p>
<p style="text-align: right;">Page 67</p> <p>1 I'm not -- you know, I am not aware of</p> <p>2 Johnson &amp; Johnson, their opinions or thoughts</p> <p>3 regarding anything of that nature.</p> <p>4 BY MR. SOILEAU:</p> <p>5 Q. Okay. That's fair.</p> <p>6 So Johnson &amp; Johnson's position</p> <p>7 or what Johnson &amp; Johnson thinks about the</p> <p>8 safety of its talcum powder products is</p> <p>9 simply a question that you were not asked to</p> <p>10 look at and have not looked at, fair?</p> <p>11 A. Again, I looked at the body of</p> <p>12 science, I looked at what the scientific</p> <p>13 evidence shows. What Johnson &amp; Johnson</p> <p>14 thought or does, you know, is separate from</p> <p>15 that. That's not something that I would be</p> <p>16 looking at when looking at the scientific</p> <p>17 evidence.</p> <p>18 Q. But as we sit here today,</p> <p>19 Doctor, you don't know what scientific</p> <p>20 evidence or what literature Johnson &amp; Johnson</p> <p>21 has itself gathered or might have in its</p> <p>22 possession, do you?</p> <p>23 MR. FROST: Objection.</p> <p>24 A. As I said, I went to the</p>	<p style="text-align: right;">Page 69</p> <p>1 Provided Documents," closed quotes.</p> <p>2 Do you see that?</p> <p>3 A. Yes, I do.</p> <p>4 Q. Are there any other provided</p> <p>5 documents that you have not identified for us</p> <p>6 as we sit here today?</p> <p>7 A. Let's see.</p> <p>8 Q. To be fair, I do have your</p> <p>9 supplemental list that we received this week,</p> <p>10 and we may look at that today.</p> <p>11 A. Yes.</p> <p>12 Q. And I understand that there's a</p> <p>13 supplemental list you have produced. We'll</p> <p>14 attach it perhaps later. It's not included</p> <p>15 in Exhibit 1, your report, but certainly</p> <p>16 those things that are on the supplemental</p> <p>17 list have been identified to us. So that's</p> <p>18 understood.</p> <p>19 A. Okay.</p> <p>20 Q. I just want to make sure that</p> <p>21 as to Other Provided Documents under</p> <p>22 Section 3.0 of your report, there's not</p> <p>23 anything that's not been identified to us as</p> <p>24 we sit here today.</p>

18 (Pages 66 to 69)

Kelly Tuttle, Ph.D.

Page 70	Page 72
<p>1 Does that make sense?</p> <p>2 A. Yes. I'm just reviewing the</p> <p>3 list to see if there's anything that comes to</p> <p>4 my mind that was provided --</p> <p>5 Q. Sure.</p> <p>6 A. -- that may have been...</p> <p>7 Q. This is my opportunity to talk</p> <p>8 to you and to be fair and complete. I would</p> <p>9 not want to be in a courtroom later and hear</p> <p>10 that, well, aha, under Section 3.0 on page 2,</p> <p>11 I said other provided documents and there</p> <p>12 were some other documents we never identified</p> <p>13 for you, and we meant to reference that</p> <p>14 through that generic language.</p> <p>15 A. Sure.</p> <p>16 Q. There's nothing like that, is</p> <p>17 there?</p> <p>18 A. No, I don't believe so. I</p> <p>19 believe everything that was provided is cited</p> <p>20 here, and then the scientific literature in</p> <p>21 my references, I'm trying to think if there</p> <p>22 was any instance where we were unable to pull</p> <p>23 an article that we had found, you know, in</p> <p>24 our PubMed searches that we went to the</p>	<p>1 At pages 4 and 5 of your</p> <p>2 report, you list and discuss the nine Hill</p> <p>3 aspects, don't you?</p> <p>4 A. Yes, I list and briefly discuss</p> <p>5 the nine Hill -- excuse me -- the nine Hill</p> <p>6 criteria.</p> <p>7 Q. Okay. Very well. Let me show</p> <p>8 you a document that I will mark as Tuttle</p> <p>9 Exhibit 7.</p> <p>10 (Whereupon, Deposition Exhibit</p> <p>11 Tuttle-7, 1965 Hill Publication, was</p> <p>12 marked for identification.)</p> <p>13 BY MR. SOILEAU:</p> <p>14 Q. Do you recognize Tuttle</p> <p>15 Exhibit 7?</p> <p>16 A. Yes, I do.</p> <p>17 Q. What is Tuttle Exhibit 7?</p> <p>18 A. So this is the 1965 Hill</p> <p>19 article entitled The Environment and Disease:</p> <p>20 Association or Causation, that I cite in my</p> <p>21 report.</p> <p>22 Q. Do you consider this sort of a</p> <p>23 seminal paper?</p> <p>24 A. It certainly is, as I state in</p>
Page 71	Page 73
<p>1 attorneys to get a copy of, but I don't think</p> <p>2 that we had to do that.</p> <p>3 Q. Okay.</p> <p>4 A. But if we had, it would have</p> <p>5 been cited in the references earlier in the</p> <p>6 report.</p> <p>7 Q. Exactly. Right. If you had</p> <p>8 run into that obstacle, it still would have</p> <p>9 made -- that is, that literature that was not</p> <p>10 immediately available to you would have made</p> <p>11 its way into the reference list that begins</p> <p>12 at page 72 of your report, correct?</p> <p>13 I didn't mean for you to check</p> <p>14 the page.</p> <p>15 A. Yes.</p> <p>16 Q. I'm just trying to identify the</p> <p>17 reference list.</p> <p>18 You put in the reference list,</p> <p>19 as supplemented by the list we got this week,</p> <p>20 all of the materials that you're relying on,</p> <p>21 fair?</p> <p>22 A. Yes.</p> <p>23 Q. Okay. Let's look at pages 4</p> <p>24 and 5 of your report, if you will.</p>	<p>1 my report, one of the -- well, I mean,</p> <p>2 obviously it's now the criteria is known as</p> <p>3 the Hill criteria, and that, with the other</p> <p>4 reference I cite, is some of the literature</p> <p>5 that established methodology for establishing</p> <p>6 whether an association is merely correlative</p> <p>7 or if it is causative.</p> <p>8 Q. You said again, known as the</p> <p>9 Hill criteria. Do you know whether Sir</p> <p>10 Austin Bradford Hill ever used the word</p> <p>11 "criteria" in this paper?</p> <p>12 A. Not off the top of my head, no,</p> <p>13 I don't know if he used that word</p> <p>14 specifically. I would need to look through</p> <p>15 it specifically for that particular word.</p> <p>16 Q. All right. You do say that</p> <p>17 Hill -- this I see at page 5 of your report.</p> <p>18 You say that Hill concludes</p> <p>19 that these nine viewpoints should be studied</p> <p>20 noting none of the viewpoints provides</p> <p>21 indisputable evidence, correct?</p> <p>22 A. Yes, I state that Sir Hill</p> <p>23 stressed that the nine viewpoints should be</p> <p>24 examined as a whole and that no -- as I said,</p>

19 (Pages 70 to 73)



Kelly Tuttle, Ph.D.

<p style="text-align: right;">Page 74</p> <p>1 no one viewpoint alone could provide 2 indisputable evidence. 3 Q. But that's not all he said, is 4 it? 5 MR. FROST: Objection. 6 BY MR. SOILEAU: 7 Q. Well, let me ask you: Didn't 8 he go on to say that while none of his nine 9 viewpoints can bring indisputable evidence 10 for or against the cause and effect 11 hypothesis, none can be required as a sine 12 qua non? 13 A. I'm sorry, can you refer me to 14 where you are in this article, please? 15 Q. Sure. Do you recognize that 16 from the Hill paper, the language I just 17 read? 18 A. I'd like to be able to see it 19 on the page, if you don't mind. 20 Q. And I'm glad to show it to you, 21 but I wanted to ask if you recognized it 22 first before we look at it in the paper. 23 Do you? 24 A. Briefly. As I said, I'd need</p>	<p style="text-align: right;">Page 76</p> <p>1 Did I read that correctly? 2 A. Yes, you did. And as I said, 3 and he says it here, the nine different 4 viewpoints must all be studied before you can 5 make a determination regarding causal 6 association, which is what I believe I said, 7 you can't pull one viewpoint, as we were 8 saying earlier, and provide from one 9 viewpoint indisputable evidence. 10 Q. Right. And the word "must" in 11 the quote I just read, that is emphasized in 12 the original paper from Sir Bradford Hill, 13 isn't it; that is, what I do not believe is 14 that we can usefully lay down some 15 hard-and-fast rules of evidence that must be 16 obeyed? He emphasized the word "must." 17 A. Yes, it is italicized here in 18 this report. 19 Q. All right. The next sentence 20 includes the "none of the nine viewpoints 21 bring indisputable evidence" that you quote 22 from in your paper, your report, correct? 23 A. Let me double-check my quote to 24 make sure it's --</p>
<p style="text-align: right;">Page 75</p> <p>1 to see it in the actual article so I can kind 2 of see the entire sentence as a whole. 3 Q. Okay. Let me -- let's look at 4 it. I'm looking at page -- it says 11 at the 5 top left and 299 to the top right. I believe 6 this comes out of an occupational medicine 7 textbook and that's why there are two 8 different page numbers. 9 Do you see page 11 at the top 10 left? 11 A. Yes, I do. 12 Q. And you see a paragraph that 13 begins with here then are nine different 14 viewpoints from all of which we could 15 study -- I'm sorry, we should study 16 association before we cry causation. 17 Do you see that? 18 A. Yes, I see that paragraph. 19 Q. And Sir Bradford Hill goes on 20 to say: What I do not believe, and this has 21 been suggested, is that we can usefully lay 22 down some hard-and-fast rules of evidence 23 that must be obeyed before we accept cause 24 and effect.</p>	<p style="text-align: right;">Page 77</p> <p>1 Q. Sure. 2 A. Yes. 3 Q. But you only used the first 4 part of this sentence which reads, quote, 5 "None of my nine viewpoints can bring 6 indisputable evidence." 7 You don't use the rest of the 8 sentence, do you, in your report? 9 A. In my report, I specifically 10 just quote the indisputable evidence words, 11 since I was taking that directly from his 12 report. 13 Q. Well, from a scientific 14 approach, Doctor, do you think it's fair to 15 quote Sir Bradford Hill on the indisputable 16 evidence that may or may not be offered by 17 any of his viewpoints and omit the language 18 where he says "none can be required as a sine 19 qua non?" 20 MR. FROST: Objection. 21 BY MR. SOILEAU: 22 Q. Do you think that's good 23 practice? 24 MR. FROST: Objection.</p>

20 (Pages 74 to 77)

Kelly Tuttle, Ph.D.

<p style="text-align: right;">Page 78</p> <p>1 A. Well, again, I think if you --</p> <p>2 as I said, I took "indisputable evidence"</p> <p>3 directly from his report, which is why it is</p> <p>4 put in quotations and cited for accuracy.</p> <p>5 BY MR. SOILEAU:</p> <p>6 Q. I understand that.</p> <p>7 A. But again, as I said, you can't</p> <p>8 take any single of these viewpoints put forth</p> <p>9 by Hill and be -- as it says, bring</p> <p>10 indisputable evidence. You can't take any</p> <p>11 single criteria in a vacuum and make a</p> <p>12 determination regarding a causal association.</p> <p>13 All nine should be studied -- should be</p> <p>14 studied, which is what he states at the</p> <p>15 beginning of that paragraph.</p> <p>16 Q. Certainly. And none can be</p> <p>17 required, fair?</p> <p>18 MR. FROST: Objection.</p> <p>19 A. As I said, he states at the</p> <p>20 beginning that all of which they should study</p> <p>21 before establishing a causal opinion.</p> <p>22 BY MR. SOILEAU:</p> <p>23 Q. Doesn't Sir Austin Bradford</p> <p>24 Hill also teach us that none can be required</p>	<p style="text-align: right;">Page 80</p> <p>1 of the nine without assessing the other nine</p> <p>2 and assessing the body of science as a whole,</p> <p>3 which is what Sir Hill is stating here when</p> <p>4 he says the nine different viewpoints from</p> <p>5 all -- all of which we should study</p> <p>6 association before we cry causation.</p> <p>7 Q. What does sine qua non mean?</p> <p>8 Do you know? How is your Latin?</p> <p>9 A. My Latin is very rusty. I took</p> <p>10 Latin in undergrad but that was a while ago.</p> <p>11 Q. You don't know what it means?</p> <p>12 A. Not off the top of my head, no.</p> <p>13 Q. Very well.</p> <p>14 Are you familiar with a</p> <p>15 textbook called Modern Epidemiology?</p> <p>16 A. Maybe vaguely.</p> <p>17 Q. Do you know who the authors</p> <p>18 are?</p> <p>19 A. No, I do not.</p> <p>20 Q. Do you know whether there is a</p> <p>21 textbook that is universally accepted in the</p> <p>22 United States as a leading textbook on</p> <p>23 epidemiology?</p> <p>24 MR. FROST: Objection.</p>
<p style="text-align: right;">Page 79</p> <p>1 before we determine cause and effect?</p> <p>2 MR. FROST: Objection.</p> <p>3 A. Again, as I said before, you</p> <p>4 can't take one in a vacuum and use one</p> <p>5 criteria to either prove or dis- -- the Hill</p> <p>6 criteria. You have to take all nine and look</p> <p>7 at the context of all nine as a whole.</p> <p>8 BY MR. SOILEAU:</p> <p>9 Q. You cannot take one criteria to</p> <p>10 prove -- you said to either prove or. Isn't</p> <p>11 it more complete and correct to say you can't</p> <p>12 take one in a vacuum, one criteria, to either</p> <p>13 prove or disprove causation?</p> <p>14 MR. FROST: Objection.</p> <p>15 A. No, I stopped myself because</p> <p>16 that's inaccurate. Scientifically, you can't</p> <p>17 prove a negative.</p> <p>18 BY MR. SOILEAU:</p> <p>19 Q. Well, okay. I'm sorry, I feel</p> <p>20 like I cut you off. I didn't mean to. Go</p> <p>21 ahead.</p> <p>22 A. Thank you.</p> <p>23 So you can't take one criteria</p> <p>24 in a vacuum, you can't take one criteria out</p>	<p style="text-align: right;">Page 81</p> <p>1 A. No, I'm not aware of that.</p> <p>2 BY MR. SOILEAU:</p> <p>3 Q. Have you heard the name Sander</p> <p>4 Greenland?</p> <p>5 A. No, I don't believe I have.</p> <p>6 Q. Have you heard the name Kenneth</p> <p>7 Rothman?</p> <p>8 A. Maybe vaguely, but I'm not</p> <p>9 familiar with him.</p> <p>10 Q. Okay. Do you own a copy of</p> <p>11 Modern Epidemiology?</p> <p>12 A. I don't believe so, no.</p> <p>13 Q. Do you know whether you ever</p> <p>14 studied a course that required the use of the</p> <p>15 textbook Modern Epidemiology in your various</p> <p>16 educational endeavors?</p> <p>17 A. I certainly studied</p> <p>18 epidemiology as part of my training and</p> <p>19 expertise in toxicology. I don't recall</p> <p>20 having a textbook on epidemiology solely.</p> <p>21 Q. All right. Let me show you an</p> <p>22 excerpt from a textbook called Modern</p> <p>23 Epidemiology, Third Edition. I will mark</p> <p>24 this as Exhibit 8.</p>

21 (Pages 78 to 81)

Kelly Tuttle, Ph.D.

<p style="text-align: right;">Page 82</p> <p>1 (Whereupon, Deposition Exhibit 2 Tuttle-8, Excerpt from Modern 3 Toxicology Third Edition, was marked 4 for identification.) 5 BY MR. SOILEAU: 6 Q. I don't suppose it does, but 7 let me just ask. Does the first page of 8 Tuttle Exhibit 8, which is the cover of the 9 textbook, happen to trigger any recollection? 10 A. No, it does not. 11 Q. All right. Then let's turn to 12 the excerpt that I have from page 26 of 13 Modern Epidemiology, and I have here just a 14 section called or labeled Causal Criteria. 15 It's under Section 1 of Basic Concepts of the 16 textbook Modern Epidemiology. 17 And I'd like you to look. You 18 see in the last paragraph of this document a 19 reference to Hill. You see that? 20 A. Yes, I do. 21 Q. And just for context, if you go 22 one paragraph up, you will see a reference as 23 well to the viewpoints proposed by Sir Austin 24 Bradford Hill dated 1965.</p>	<p style="text-align: right;">Page 84</p> <p>1 Q. Okay. I want to read to you 2 the end of this paragraph from the Modern 3 Epidemiology textbook. It says: Hill 4 emphasized that causal inferences cannot be 5 based on a set of rules, condemned emphasis 6 on statistical significance testing, and 7 recognized the importance of many other 8 factors in decision-making, citing Phillips 9 and Goodman, 2004. Nonetheless, the 10 misguided but popular view that his 11 considerations should be used as criteria for 12 causal inference makes it necessary to 13 examine them in detail. 14 Do you agree or disagree with 15 that summary statement about Hill? 16 MR. FROST: Objection. 17 A. Well -- 18 BY MR. SOILEAU: 19 Q. Or I'm sorry, or if you're not 20 able to offer a comment, certainly that can 21 be the answer. It need not be 22 agree/disagree. It can be I don't have an 23 answer or position. 24 Go ahead, I'm sorry.</p>
<p style="text-align: right;">Page 83</p> <p>1 A. Yes, I see that. 2 Q. And if we come back down to the 3 final paragraph, you see that the nine 4 viewpoints are included in the middle of that 5 paragraph? 6 A. Yes, I see them listed. 7 Q. Okay. We're talking about the 8 same paper that is now Tuttle Exhibit 7, 9 correct? 10 A. I believe so. I would need to 11 look at the references to be specific. I 12 don't know if Sir Hill published anything 13 else in that year. 14 Q. Okay. Very well. 15 Can we agree that the nine 16 viewpoints that are listed in the final 17 paragraph of Tuttle Exhibit 8 are identical 18 to the nine viewpoints that you included in 19 your report beginning at pages 4 and 5? 20 Do you need to check them? 21 A. I'm just looking to make sure 22 that the wording is the same. 23 Q. Absolutely. Do that. 24 A. Yes, I believe so.</p>	<p style="text-align: right;">Page 85</p> <p>1 A. As I said, I'm not familiar 2 with this textbook. The statement regarding 3 Hill does not cite Hill's work; it cites 4 another article that I'm not familiar with 5 and don't know the title. I would need to 6 see that article, the basis for that 7 statement, before I could provide any 8 discussion on it. 9 Q. Okay. And in fairness to you, 10 you're not really familiar with these 11 authors, Rothman, Greenland and Lash, to 12 react to the fact that it's their textbook, 13 fair? 14 A. No. As I said, I'm not 15 familiar with this textbook and I'm not 16 familiar with the authors. 17 Q. Okay. Very well. 18 Let's focus for a few minutes, 19 if we could -- I'm going to check. 20 MR. SOILEAU: Everybody doing 21 okay time-wise, break-wise, my 22 reporter? All right. If someone 23 needs a break, let me know. 24 Otherwise, we'll keep going.</p>

22 (Pages 82 to 85)

Kelly Tuttle, Ph.D.

<p style="text-align: right;">Page 86</p> <p>1 THE WITNESS: I'm nearing the 2 time I will need a break, just a very 3 brief one. 4 MR. SOILEAU: You want to go 5 ahead and take it now? It's a stop 6 spot. Let's do that. Let's take a 7 quick break. We'll go off the record. 8 THE VIDEOGRAPHER: Going off 9 record, 10:24 a.m. 10 (Recess taken, 10:24 a.m. to 11 10:34 a.m.) 12 THE VIDEOGRAPHER: We're back 13 on the record at 10:34 a.m. 14 BY MR. SOILEAU: 15 Q. Okay. Doctor, we had a short 16 break. Are you ready to proceed? 17 A. Yes, I am. 18 Q. Very well. 19 Let's focus on one of the 20 Hugh -- that's going to be tough because none 21 of us have looked at Hugh. 22 Let's look at one of the Hill 23 viewpoints, okay? Plausibility. 24 You say at page 30 of your</p>	<p style="text-align: right;">Page 88</p> <p>1 ovarian cancer relies solely on the proximity 2 of talc particles to the ovaries, and the 3 proposed migration to the ovaries. 4 Did I read that sentence 5 correctly? 6 A. Yes, you read that sentence 7 correctly. I believe I discuss -- I state in 8 the next sentence I discuss it in greater 9 detail later in the report. 10 Q. Sure. 11 When you say in that sentence, 12 Doctor, the proximity of talc particles to 13 the ovaries, what do you mean? 14 A. So I'm referring to the 15 hypothesis that perineal application of 16 talcum powder can migrate from the perineum 17 to the ovaries. 18 Q. Do you agree that perineal 19 application of talcum powder will put talc 20 particles and talcum powder in proximity to 21 the ovaries? 22 MR. FROST: Objection. 23 A. Again, as I discuss in my 24 report, the scientific evidence has not</p>
<p style="text-align: right;">Page 87</p> <p>1 report, in part: The plausibility of a 2 relationship -- let me let you get there. Do 3 you see it? 4 A. Yes, I'm there. 5 Q. Okay. On page 30 you have a 6 subheading for one of the Hill viewpoints and 7 that is plausibility, which I believe is 8 number 6, correct? 9 A. Of the -- 10 Q. Of the nine. 11 A. I don't apply a number to them, 12 but it looks like it's number six as far as 13 the list. 14 Q. I tell you what. Look at 15 page 5 of your report for a moment. Do you 16 see plausibility there? 17 A. Yes. 18 Q. It's number 6? 19 A. Yes, it's listed as number 6. 20 Q. Very good. Let's go back to 21 page 30 now of your report, if we could. And 22 under the subheading Plausibility, you say in 23 part, and I will quote: The plausibility of 24 a relationship between talc exposure and</p>	<p style="text-align: right;">Page 89</p> <p>1 established that perineal application of 2 talcum powder will allow talcum particles to 3 migrate from the genital area to the ovaries. 4 BY MR. SOILEAU: 5 Q. Okay. So the issue you have is 6 with the idea of migration, fair? 7 A. What I address in my report is 8 the hypothesis that the perineal application 9 of talcum powder will allow talc particles to 10 migrate from the genital area to the ovaries. 11 Q. How did the talcum particles -- 12 let me restate that. 13 How do the talc particles come 14 to be in close proximity to the ovaries? 15 MR. FROST: Objection. 16 BY MR. SOILEAU: 17 Q. Do you have an understanding? 18 A. Well, as I said for -- for -- 19 as I'm discussing in this report and as I 20 discuss later in the report, I am examining 21 the scientific evidence for the hypothesis 22 that external application of talcum powder to 23 the genital area will allow talc particles to 24 migrate through the female reproductive tract</p>

23 (Pages 86 to 89)

Kelly Tuttle, Ph.D.

<p style="text-align: right;">Page 90</p> <p>1 to the ovaries.</p> <p>2 Q. Why do you say talc particles</p> <p>3 as opposed to talcum powder?</p> <p>4 A. Because that's what I refer to</p> <p>5 specifically in my report and in assessing</p> <p>6 some of the scientific literature, they're</p> <p>7 looking for talc particles in the ovaries,</p> <p>8 and so that's why I used the term "talc</p> <p>9 particles."</p> <p>10 Q. Okay. So your statement here</p> <p>11 that plausibility relies solely on something,</p> <p>12 it's really that the plausibility of a</p> <p>13 relationship relies solely on the proposed</p> <p>14 migration theory? Is that a fair summary of</p> <p>15 what you're telling us there?</p> <p>16 MR. FROST: Objection.</p> <p>17 BY MR. SOILEAU:</p> <p>18 Q. You say solely and then I see</p> <p>19 talc particles in proximity to the ovaries</p> <p>20 and proposed migration. I see more than one</p> <p>21 thing. I just want to understand what you</p> <p>22 mean when you say relies solely on. Relies</p> <p>23 solely on what?</p> <p>24 A. So in relation to the -- again,</p>	<p style="text-align: right;">Page 92</p> <p>1 will, is what you're telling me?</p> <p>2 MR. FROST: Objection.</p> <p>3 A. I'm saying that the mere</p> <p>4 presence of a particle or chemical or</p> <p>5 anything when looking at toxicology, the mere</p> <p>6 presence of a material does not mean that the</p> <p>7 material will cause an adverse effect on the</p> <p>8 tissue or organ that it's located at.</p> <p>9 BY MR. SOILEAU:</p> <p>10 Q. But it might?</p> <p>11 MR. FROST: Objection.</p> <p>12 A. Again, it depends. You have to</p> <p>13 look at the scientific evidence, you have to</p> <p>14 look at the scientific literature, you have</p> <p>15 to look at dose and frequency of exposures</p> <p>16 and all those different parameters.</p> <p>17 BY MR. SOILEAU:</p> <p>18 Q. Okay. I'll tell you what.</p> <p>19 We'll come back to that issue in a moment.</p> <p>20 I meant to ask you: How many</p> <p>21 hours have you spent with the J&amp;J attorneys</p> <p>22 thus far during this project?</p> <p>23 A. I couldn't give you an exact</p> <p>24 number. I would estimate we have probably</p>
<p style="text-align: right;">Page 91</p> <p>1 the assessment of the scientific literature</p> <p>2 regarding perineal application of talcum</p> <p>3 powder and ovarian cancer there is the</p> <p>4 proposed migration that the external perineal</p> <p>5 application of talcum powder will cause talc</p> <p>6 particles to migrate throughout the female</p> <p>7 reproductive tract to the ovaries.</p> <p>8 And secondarily to that is that</p> <p>9 the presence of talc particles at the ovaries</p> <p>10 is -- I'm sorry, I'm trying to make sure I'm</p> <p>11 speaking very clearly -- that the presence of</p> <p>12 talc particles at the ovaries is sufficient</p> <p>13 to -- or insufficient to establish a causal</p> <p>14 association with ovarian cancer.</p> <p>15 Q. Would the presence of talc</p> <p>16 particles at the ovaries be important from</p> <p>17 your perspective as a toxicologist?</p> <p>18 MR. FROST: Objection.</p> <p>19 A. Well, again, not assessing</p> <p>20 necessarily the migration, the presence of a</p> <p>21 material at an organ or at a tissue does not</p> <p>22 mean that it will exert an adverse effect.</p> <p>23 BY MR. SOILEAU:</p> <p>24 Q. Well, it doesn't mean that it</p>	<p style="text-align: right;">Page 93</p> <p>1 spent between 20 and 25 hours together.</p> <p>2 Q. Okay. That includes the time</p> <p>3 yesterday?</p> <p>4 A. Yes.</p> <p>5 Q. Let me show you a couple of</p> <p>6 exhibits that I will mark separately as</p> <p>7 Tuttle Exhibit 9 and Tuttle Exhibit 10.</p> <p>8 (Whereupon, Deposition Exhibit</p> <p>9 Tuttle-9, CTEH Billing Summary, was</p> <p>10 marked for identification.)</p> <p>11 (Whereupon, Deposition Exhibit</p> <p>12 Tuttle-10, CTEH Billing Summary, was</p> <p>13 marked for identification.)</p> <p>14 BY MR. SOILEAU:</p> <p>15 Q. Take a look at these two</p> <p>16 documents and identify them for me.</p> <p>17 MR. SOILEAU: And for the</p> <p>18 purposes of counsel --</p> <p>19 MR. FROST: I was going to say,</p> <p>20 do you mind telling me which one is 9</p> <p>21 and which one is 10?</p> <p>22 MR. SOILEAU: Exactly.</p> <p>23 BY MR. SOILEAU:</p> <p>24 Q. Why don't you help us because</p>



Kelly Tuttle, Ph.D.

<p style="text-align: right;">Page 94</p> <p>1 you have them there as I've already marked 2 them. 3 A. So these -- I'm sorry. 4 Q. Yes. 5 MR. SOILEAU: Before you do 6 that, we have different invoice 7 numbers. And, Mr. Frost, if you can 8 look over at Exhibit 9 and if you'll 9 look at the invoice number and tell us 10 which one is Exhibit 9 and which one 11 is Exhibit 10 so I don't get it wrong. 12 MR. FROST: Exhibit 9 is 13 316304. 14 MR. SOILEAU: Very good. And 15 then I will deduce that the other one 16 is 10. 17 MR. FROST: I'm going to make 18 the same assumption. 19 BY MR. SOILEAU: 20 Q. Very good. 21 Okay, Doctor, and I apologize 22 for interrupting you. Go ahead. You were 23 going to tell me what these are. 24 A. These are invoices provided by</p>	<p style="text-align: right;">Page 96</p> <p>1 A. So all of our time is billed 2 and documented in our invoices. 3 Q. Right. But how do I know whose 4 time I'm looking at? 5 A. The first page is just a 6 summary of the hours that were billed that 7 particular day, and in the subsequent pages, 8 they break that down by employee. 9 Q. Right. But you see that my 10 copy is redacted. 11 A. Yes, I do. 12 Q. Is there any way for me to know 13 the names of the folks at CTEH who have 14 worked on this Johnson &amp; Johnson Daubert 15 challenge project? 16 A. It would be -- I could probably 17 tell you most of them. We have a team that 18 supports -- I have a team that has supported 19 me in my drafting of my report in this case, 20 and that's their additional time that would 21 be itemized in this invoice. 22 Q. All right. Do that for me, if 23 you would, if you would give me names and 24 titles or job positions. I know you gave us</p>
<p style="text-align: right;">Page 95</p> <p>1 CTEH regarding my work on the Johnson &amp; 2 Johnson Daubert challenge. 3 Q. The Johnson &amp; Johnson Daubert 4 challenge. 5 Is this, to your knowledge, the 6 only file that CTEH has opened for Johnson &amp; 7 Johnson? 8 A. To my knowledge, yes. I don't 9 know what other individuals in the company 10 are working on, but to my knowledge, yes. 11 Q. Well, fair. But -- I think 12 we're together. 13 As we sit here, you don't have 14 any knowledge and you're not aware of anyone 15 else working at CTEH on a Johnson &amp; Johnson 16 talcum powder project other than the team 17 that's worked with you on this Johnson &amp; 18 Johnson Daubert challenge; is that fair? 19 A. I'm sorry, can you restate 20 that? I got a little confused there towards 21 the end. 22 Q. Yeah. I'll come back to it. 23 How do I know who all at CTEH 24 has worked on this project?</p>	<p style="text-align: right;">Page 97</p> <p>1 one already. You gave us Samantha Nation? 2 A. Nation. 3 Q. And she was an information 4 specialist? 5 A. Yes. 6 Q. Do you happen to know her rate? 7 A. Not off the top of my head, no. 8 Q. Okay. Who else has worked on 9 this project at CTEH? 10 A. So in addition to Samantha, we 11 have also had a health scientist, Dana 12 Cubanski. 13 Q. How do you spell her last name? 14 A. C-U-B-A-N-S-K-I. 15 Q. Very well. 16 And what does that mean, health 17 scientist? How is she degreed, for example? 18 A. She -- and I don't remember 19 specifically. She has a master's in science. 20 I don't remember her exact field for her 21 degree. 22 Q. All right. Who else? 23 A. In addition to Dana, Dr. Scott 24 Malm, M-A-L-M, who is a toxicologist.</p>

25 (Pages 94 to 97)

Kelly Tuttle, Ph.D.

<p style="text-align: right;">Page 98</p> <p>1 Q. What role does he play on this?</p> <p>2 A. He just provided some support</p> <p>3 for me reviewing my report, you know, looking</p> <p>4 at presentation, you know, typos, you know,</p> <p>5 checking, double-checking the report for me.</p> <p>6 Q. Sort of a peer review? Not</p> <p>7 formally, but sort of?</p> <p>8 A. Not really a peer review.</p> <p>9 Mainly just assisting with looking at</p> <p>10 formatting, presentation issues, making --</p> <p>11 trying to help make sure when you're writing</p> <p>12 a report and dealing with something of this</p> <p>13 size, making sure there's no typos or making</p> <p>14 sure that I don't use inappropriate</p> <p>15 punctuation or my sentences end and I don't</p> <p>16 just kind of jump off onto another thought</p> <p>17 process or things like that.</p> <p>18 Q. But he is a Ph.D. toxicologist?</p> <p>19 A. Yes, he is.</p> <p>20 Q. If I were comparing the two of</p> <p>21 you on some sort of company chart, is one</p> <p>22 superior or -- to the other, overseeing the</p> <p>23 other, or are you sort of on parallel</p> <p>24 platforms?</p>	<p style="text-align: right;">Page 100</p> <p>1 A. I think all that's left is some</p> <p>2 support staff who assisted with organizing</p> <p>3 the file of materials, you know, with the</p> <p>4 references and things like that.</p> <p>5 Q. Is their time billed as well?</p> <p>6 A. I believe so, yes.</p> <p>7 Q. Okay. Their work would have</p> <p>8 been clerical or administrative, as opposed</p> <p>9 to substantive?</p> <p>10 A. Yes.</p> <p>11 Q. They were not reviewing your</p> <p>12 report or your work or your opinions and</p> <p>13 offering substantive comment, were they?</p> <p>14 A. No, they were not. And as I</p> <p>15 said earlier, you know, those who did review</p> <p>16 my report were reviewing it for, you know,</p> <p>17 clarity, for presentation issues, for</p> <p>18 punctuation, formatting, things of that</p> <p>19 nature.</p> <p>20 Q. Right. I was just really</p> <p>21 referring to that last group of people who</p> <p>22 are thus far unidentified and understanding</p> <p>23 their role as more administrative or</p> <p>24 clerical. That's fair, right?</p>
<p style="text-align: right;">Page 99</p> <p>1 A. I don't oversee Dr. Malm. He</p> <p>2 has been with the company for a shorter</p> <p>3 period of time than I, but beyond that,</p> <p>4 there's no --</p> <p>5 Q. Y'all are just colleagues?</p> <p>6 A. Yes.</p> <p>7 Q. Who else?</p> <p>8 A. Dr. Michael Reilly.</p> <p>9 Q. Last name?</p> <p>10 A. R-E-I-L-L-Y, I believe.</p> <p>11 Q. All right. And his position?</p> <p>12 A. He is also a toxicologist.</p> <p>13 Q. Simply another colleague to you</p> <p>14 and Dr. Malm?</p> <p>15 A. Yes.</p> <p>16 Q. And he is a Ph.D. toxicologist?</p> <p>17 A. Yes, he is.</p> <p>18 Q. And what role did Dr. Reilly</p> <p>19 have?</p> <p>20 A. He did the same type of support</p> <p>21 work for me as Dr. Malm.</p> <p>22 Q. Any others at CTEH who have</p> <p>23 worked on this Johnson &amp; Johnson Daubert</p> <p>24 challenge project?</p>	<p style="text-align: right;">Page 101</p> <p>1 A. Yes, that's fair.</p> <p>2 Q. And I didn't mean to include,</p> <p>3 just so that we are together, Dr. Malm or the</p> <p>4 other persons at CTEH who may have worked</p> <p>5 with you.</p> <p>6 Is there any way for me to look</p> <p>7 at Exhibit 9 and Exhibit 10 and know, for</p> <p>8 example, how many hours you have?</p> <p>9 A. With the numbers redacted --</p> <p>10 Q. I'm sorry, the what?</p> <p>11 A. I'm sorry, not the numbers</p> <p>12 redacted. With the names and times redacted,</p> <p>13 generally speaking, looking at Exhibit 9, I</p> <p>14 believe right here at the page 3 of 4 and</p> <p>15 page 4, where the hourly rate put forth by</p> <p>16 CTEH is listed as \$305 an hour, that would be</p> <p>17 my time that I billed for this particular</p> <p>18 invoice.</p> <p>19 Q. Would Dr. Malm, for example,</p> <p>20 have the same rate?</p> <p>21 A. No, he would not.</p> <p>22 Q. What is his rate?</p> <p>23 A. I don't know specifically.</p> <p>24 Q. Are you the only person at CTEH</p>

Kelly Tuttle, Ph.D.

<p style="text-align: right;">Page 102</p> <p>1 who worked on the Johnson &amp; Johnson Daubert 2 challenge project who billed at \$305 an hour? 3 A. I believe so, yes. 4 Q. So to your understanding, I can 5 at least look for the itemized pages, look at 6 the rate, and when I see \$305 an hour, you 7 would suggest I could assume correctly that 8 that is you? 9 A. Yes, I believe so. 10 Q. And as to the other rates 11 shown, I could correctly assume at least that 12 it is someone other than you, someone at CTEH 13 other than you, fair? 14 A. Yes, that's correct. 15 Q. Okay. Let me show you 16 something we made reference to earlier and 17 I'll make part of our record, marked as 18 Exhibit 11. 19 (Whereupon, Deposition Exhibit 20 Tuttle-11, Tuttle Supplemental 21 Materials Reviewed and Considered, was 22 marked for identification.) 23 BY MR. SOILEAU: 24 Q. It's a one-page document.</p>	<p style="text-align: right;">Page 104</p> <p>1 these from that broader library? 2 A. I believe the attorneys 3 provided all of the defense expert reports 4 that are related to the MDL litigation. 5 These are the subset that I read specifically 6 or reviewed specifically. I don't believe I 7 received all of the depositions, but I think 8 I received -- but the ones that I reviewed 9 are provided here. 10 Q. Okay. There are 12 items 11 listed on Tuttle Exhibit 11? 12 A. Yes. 13 Q. And I believe each one of the 14 12 is either a deposition or an expert 15 report, with the exception of item 11. 16 Agree? 17 A. Yes, that's correct. 18 Q. How did 11, the Taher, 19 T-A-H-E-R, the Taher paper, come to be among 20 the supplemental materials reviewed and 21 considered? 22 MR. FROST: Objection. 23 A. It was discussed in the 24 Health Canada draft assessment that I</p>
<p style="text-align: right;">Page 103</p> <p>1 Do you recognize this document, 2 Doctor? 3 A. Yes, I do. 4 Q. And this is the supplemental 5 materials reviewed and considered? 6 A. Yes, it is. 7 Q. And how was it determined to 8 your knowledge what supplemental materials 9 you would review and consider? 10 MR. FROST: Objection. 11 BY MR. SOILEAU: 12 Q. I'm just asking you -- how 13 about this so that we don't step into 14 anything we're not supposed to step into. 15 Who determined what 16 supplemental materials you were to look at? 17 A. I did. As far as, I believe, 18 all the materials provided here were ones 19 that I read or reviewed. 20 Q. Did you -- I'm sorry, go ahead. 21 A. No. And so they were ones that 22 I chose to read and review. 23 Q. Okay. Did you have a greater 24 library of documents available and select</p>	<p style="text-align: right;">Page 105</p> <p>1 mentioned in my report, and it was discussed 2 in, I believe, at least one if not other -- 3 other depositions, and I did not have a copy 4 as it's unpublished, so I can't access it in 5 the peer-reviewed literature. 6 BY MR. SOILEAU: 7 Q. Okay. You had, in preparing 8 your original report, looked at 9 Health Canada, the draft assessment from 10 Health Canada? 11 A. Yes, I cite it in my report. 12 Q. Okay. And so when you signed 13 your report, you would have been aware of the 14 Taher paper, fair? 15 A. As I said, I saw that it was 16 cited in the Health Canada draft assessment, 17 but as it's unpublished, it was inaccessible 18 in the peer-reviewed scientific literature. 19 Q. Okay. And you had seen that 20 before you signed your report, fair? 21 A. The Health Canada draft 22 assessment, yes. 23 Q. Right. And the reference to 24 Taher, the unpublished paper?</p>

27 (Pages 102 to 105)



Kelly Tuttle, Ph.D.

<p style="text-align: right;">Page 106</p> <p>1 A. Yes, I saw the reference in the</p> <p>2 Health Canada report.</p> <p>3 Q. Okay. Had you requested the</p> <p>4 Taher paper before you signed your report?</p> <p>5 A. I don't believe so, no.</p> <p>6 Q. What caused you to decide to</p> <p>7 request the Taher paper after you signed your</p> <p>8 report?</p> <p>9 A. As I said, it was unpublished,</p> <p>10 so that's why it would not have been included</p> <p>11 in my review of the scientific literature.</p> <p>12 It was included later because, as I said, I</p> <p>13 saw that it had been discussed more in</p> <p>14 detail, and so -- and since I couldn't</p> <p>15 receive a copy of it through normal</p> <p>16 scientific literature means, the attorneys</p> <p>17 provided me a copy.</p> <p>18 Q. You said you saw that it had</p> <p>19 been discussed more in detail. Where?</p> <p>20 A. I don't recall specifically,</p> <p>21 but in some of these supplemental materials</p> <p>22 that I reviewed.</p> <p>23 Q. Some of the supplemental</p> <p>24 materials listed on Tuttle Exhibit 11?</p>	<p style="text-align: right;">Page 108</p> <p>1 particularly in the heading, you do say that</p> <p>2 Dr. Plunkett's migration theory is, in your</p> <p>3 opinion, severely flawed, correct?</p> <p>4 A. 11.5 does state Dr. Plunkett's</p> <p>5 theory of particle migration from the genital</p> <p>6 area to the ovary has not been accomplished</p> <p>7 in the scientific literature and is severely</p> <p>8 flawed.</p> <p>9 Q. Very well.</p> <p>10 Turn to page 60 of your report.</p> <p>11 You say in Section 12.2 of your report,</p> <p>12 referring to Dr. Zelikoff, that the opinion</p> <p>13 that talcum powder can reach the ovaries by</p> <p>14 means of migration through the female</p> <p>15 reproductive tract after perineal application</p> <p>16 is not scientifically sound, correct?</p> <p>17 MR. FROST: Objection.</p> <p>18 A. Can you --</p> <p>19 BY MR. SOILEAU:</p> <p>20 Q. Do you say that -- sure. I can</p> <p>21 help you find it if you need me to. I'm</p> <p>22 asking you if you labeled Dr. Zelikoff's</p> <p>23 opinion on migration as not scientifically</p> <p>24 sound.</p>
<p style="text-align: right;">Page 107</p> <p>1 A. Yes.</p> <p>2 Q. During your preparation for</p> <p>3 your deposition testimony, have you been</p> <p>4 videotaped?</p> <p>5 MR. FROST: Objection.</p> <p>6 She can answer.</p> <p>7 MR. SOILEAU: Okay.</p> <p>8 A. No, I have not.</p> <p>9 BY MR. SOILEAU:</p> <p>10 Q. Okay. Let's turn to the issue</p> <p>11 of migration. You say at page 57 of your</p> <p>12 report, Section 11.5, that Dr. Plunkett's</p> <p>13 migration theory whereby talc particles</p> <p>14 supposedly migrate through the body either</p> <p>15 through perineal application or inhalation,</p> <p>16 and arrive at foreign tissues such as the</p> <p>17 ovaries, is severely flawed.</p> <p>18 Did I read that correctly from</p> <p>19 your report? Did you find it in time?</p> <p>20 A. I got to the page, but you were</p> <p>21 about halfway through the sentence.</p> <p>22 Q. All right. Let's just see if</p> <p>23 we can agree on this.</p> <p>24 At Section 11.5, and I think</p>	<p style="text-align: right;">Page 109</p> <p>1 MR. FROST: Objection.</p> <p>2 A. In the first paragraph under</p> <p>3 12.2, I say: In her expert report,</p> <p>4 Dr. Zelikoff opines that talcum powder can</p> <p>5 reach the ovaries by means of migration</p> <p>6 through the female reproductive tract after</p> <p>7 perineal application as well as through</p> <p>8 inhalation. Neither opinion is</p> <p>9 scientifically sound.</p> <p>10 BY MR. SOILEAU:</p> <p>11 Q. Okay. So it is correct that</p> <p>12 you have labeled Dr. Zelikoff's opinion on</p> <p>13 migration as not scientifically sound and</p> <p>14 Dr. Plunkett's theory of migration as</p> <p>15 severely flawed, correct?</p> <p>16 A. It's stated as not</p> <p>17 scientifically supported, as stated in my</p> <p>18 report.</p> <p>19 Q. Are those things synonymous to</p> <p>20 you?</p> <p>21 A. I'm sorry, what things?</p> <p>22 Q. Not scientifically supported</p> <p>23 and unsound or severely flawed, are all of</p> <p>24 those three things synonymous for you in</p>

28 (Pages 106 to 109)

Kelly Tuttle, Ph.D.

<p style="text-align: right;">Page 110</p> <p>1 your -- in your -- when you use those words?</p> <p>2 A. So in looking at Dr. Plunkett</p> <p>3 and Dr. Zelikoff in regards to migration,</p> <p>4 it's looking at the methodology applied and</p> <p>5 looking at the scientific evidence that</p> <p>6 supports or doesn't support their statements,</p> <p>7 and what I am saying here is that based on</p> <p>8 the scientific evidence, there's no</p> <p>9 scientific evidence that establishes that</p> <p>10 perineal application of talcum powder can</p> <p>11 migrate through the female reproductive tract</p> <p>12 and reach the ovaries.</p> <p>13 Q. No scientific evidence to</p> <p>14 establish that perineal application of talcum</p> <p>15 powder can migrate to the ovaries; is that</p> <p>16 correct?</p> <p>17 A. I believe I said no scientific</p> <p>18 evidence that supports that perineal</p> <p>19 application of talcum powder can migrate</p> <p>20 through the reproductive tract to the</p> <p>21 ovaries.</p> <p>22 Q. Thank you. No scientific</p> <p>23 evidence that supports that perineal</p> <p>24 application of talcum powder can migrate.</p>	<p style="text-align: right;">Page 112</p> <p>1 regards to talc particles based on, you know,</p> <p>2 looking at some of the scientific literature</p> <p>3 that looks at talc particles.</p> <p>4 Q. Very well.</p> <p>5 Doctor, have you formed an</p> <p>6 opinion that migration of talcum powder to</p> <p>7 the ovaries after perineal application is not</p> <p>8 plausible?</p> <p>9 MR. FROST: Objection.</p> <p>10 A. So what I did was assess the</p> <p>11 body of science to see what the scientific</p> <p>12 evidence supports, and the scientific</p> <p>13 evidence does not support the hypothesis that</p> <p>14 perineal application of talcum powder can</p> <p>15 cause talcum powder to migrate from the</p> <p>16 genital area to the ovaries.</p> <p>17 BY MR. SOILEAU:</p> <p>18 Q. You brought up the issue of</p> <p>19 migration in your report, specifically under</p> <p>20 the topic of Hill's plausibility viewpoint,</p> <p>21 didn't you?</p> <p>22 A. Yes, I did.</p> <p>23 Q. Do you have an opinion on</p> <p>24 whether migration is a plausible explanation?</p>
<p style="text-align: right;">Page 111</p> <p>1 And what you're saying is, is</p> <p>2 that no scientific evidence to support this</p> <p>3 idea that after perineal application, the</p> <p>4 talcum powder can migrate through the</p> <p>5 reproductive tract to the ovaries?</p> <p>6 A. As I said, there's no</p> <p>7 scientific evidence to support that perineal</p> <p>8 application of talcum powder will migrate</p> <p>9 from the genital area through the female</p> <p>10 reproductive tract to the ovaries.</p> <p>11 Q. Right. I guess I was just</p> <p>12 understanding. I think it's clear the thing</p> <p>13 that migrates would be the talcum powder</p> <p>14 product; is that right?</p> <p>15 You talk about perineal</p> <p>16 application of talcum powder and then you</p> <p>17 talk about migration from the genital area</p> <p>18 through the reproductive tract to the</p> <p>19 ovaries. What's migrating under this theory</p> <p>20 as you understand it?</p> <p>21 A. Under the hypothesis as I</p> <p>22 understand it is that the talcum powder would</p> <p>23 migrate through the female reproductive</p> <p>24 tract, or as I state, we discussed earlier in</p>	<p style="text-align: right;">Page 113</p> <p>1 MR. FROST: Objection.</p> <p>2 A. Well, as I said, it's not about</p> <p>3 my opinions about what the scientific</p> <p>4 evidence shows, and the scientific evidence</p> <p>5 doesn't support that, that mechanism.</p> <p>6 BY MR. SOILEAU:</p> <p>7 Q. Have you conducted a thorough</p> <p>8 review of the available scientific evidence</p> <p>9 and then formed an opinion on migration based</p> <p>10 upon that review?</p> <p>11 A. Well, as I said, I assessed the</p> <p>12 body of science, and as we discussed earlier,</p> <p>13 it's impossible to say out of the millions of</p> <p>14 scientific literature that I reviewed every</p> <p>15 single article in the realm of scientific</p> <p>16 literature, but I looked at the body of</p> <p>17 science and saw -- assessed it in the context</p> <p>18 of the Hill criteria and found that it does</p> <p>19 not support the hypothesis that perineal</p> <p>20 application of talcum powder can migrate from</p> <p>21 the genital area to the ovaries.</p> <p>22 Q. What I understand you to be</p> <p>23 telling me is that you did not find</p> <p>24 scientific evidence to support the migration</p>

Kelly Tuttle, Ph.D.

<p style="text-align: right;">Page 114</p> <p>1 theory.</p> <p>2 Have I understood you</p> <p>3 correctly?</p> <p>4 A. Yes, I believe so. As I --</p> <p>5 just to reiterate for clarity, in assessing</p> <p>6 the body of science, I found no scientific</p> <p>7 studies that supported the perineal</p> <p>8 application of talcum powder that could</p> <p>9 migrate from the genital area to the ovaries.</p> <p>10 Q. In your evaluation of the</p> <p>11 scientific evidence, did you conclude that</p> <p>12 the plausibility viewpoint fails on that</p> <p>13 basis?</p> <p>14 MR. FROST: Objection.</p> <p>15 A. I would need to return back to</p> <p>16 get my exact wording regarding the</p> <p>17 plausibility on page 30.</p> <p>18 BY MR. SOILEAU:</p> <p>19 Q. Go ahead and do that, and I'll</p> <p>20 reset my question.</p> <p>21 You had discussed with me</p> <p>22 earlier the nine viewpoints that Sir Austin</p> <p>23 Bradford Hill provided in his 1965 paper,</p> <p>24 correct?</p>	<p style="text-align: right;">Page 116</p> <p>1 satisfy plausibility under the Hill</p> <p>2 viewpoints?</p> <p>3 A. So as I note in Section 30 and</p> <p>4 as I discuss elsewhere in my report, the</p> <p>5 scientific evidence -- there's no scientific</p> <p>6 evidence to support that migration theory</p> <p>7 that perineal application of talcum powder</p> <p>8 applied to the genital area can migrate</p> <p>9 through the female reproductive tract to the</p> <p>10 ovaries.</p> <p>11 Q. Okay. And I'm sorry if you</p> <p>12 told me this before, but this issue of</p> <p>13 migration is one of the things that you</p> <p>14 reviewed as you did your overall literature</p> <p>15 search, correct?</p> <p>16 A. Yes, that's correct.</p> <p>17 Q. And to be complete, I</p> <p>18 understand you've told me that there are</p> <p>19 thousands of papers, the possibility of</p> <p>20 missing one is there, and I understand also</p> <p>21 that your review of literature was not</p> <p>22 limited to migration. That's fair as well?</p> <p>23 A. Yes, that's accurate.</p> <p>24 Q. Okay. I just wanted to make</p>
<p style="text-align: right;">Page 115</p> <p>1 A. Yes.</p> <p>2 Q. And you had stressed -- or</p> <p>3 said -- maybe stressed is unfair, but you had</p> <p>4 specifically said at some point that each of</p> <p>5 those nine viewpoints should be considered,</p> <p>6 correct?</p> <p>7 A. Yes, that's accurate. I said</p> <p>8 we should look at all nine criteria as a</p> <p>9 whole for the context, and that you can't</p> <p>10 take one criteria in a vacuum.</p> <p>11 Q. Right. But the application of</p> <p>12 Hill methodology would include a review of</p> <p>13 each of the viewpoints as part of the whole</p> <p>14 application of the methodology.</p> <p>15 Do I have it right?</p> <p>16 A. Yes, that's correct.</p> <p>17 Q. Okay. And your paper includes</p> <p>18 the plausibility viewpoint, a discussion of</p> <p>19 plausibility?</p> <p>20 A. Yes, it does.</p> <p>21 Q. So did the scientific evidence</p> <p>22 that you looked at -- that you looked at as</p> <p>23 you reviewed the literature and the available</p> <p>24 scientific evidence satisfy or fail to</p>	<p style="text-align: right;">Page 117</p> <p>1 sure it included migration. I appreciate</p> <p>2 your patience with my questions.</p> <p>3 In looking at the body of your</p> <p>4 report, I found three things that you listed</p> <p>5 in opposition to this theory of migration.</p> <p>6 One of them was gravity, is that correct,</p> <p>7 that you list gravity as a fact that stands</p> <p>8 in opposition to the migration theory?</p> <p>9 MR. FROST: Objection.</p> <p>10 A. I need to -- refer to me -- or</p> <p>11 sorry -- refer me specifically to where I</p> <p>12 discuss gravity. I do know that I mention</p> <p>13 gravity. I don't know that I present it as a</p> <p>14 fact in opposition of the migration theory.</p> <p>15 As I said, I looked at the body</p> <p>16 of science and found the scientific evidence</p> <p>17 does not support the migration theory.</p> <p>18 BY MR. SOILEAU:</p> <p>19 Q. Okay. When you review a body</p> <p>20 of scientific literature in general, do you</p> <p>21 weigh available evidence as part of your</p> <p>22 methodology?</p> <p>23 A. It depends. You know, I look</p> <p>24 at the body of science as a whole. In this</p>

30 (Pages 114 to 117)

Kelly Tuttle, Ph.D.

<p style="text-align: right;">Page 118</p> <p>1 particular case, you know, we -- I cite the</p> <p>2 available scientific literature as well as</p> <p>3 discussing issues that may be part of the</p> <p>4 study or the body -- you know, how the</p> <p>5 scientific study was performed.</p> <p>6 But generally speaking, I try</p> <p>7 to look at all -- everything that's been</p> <p>8 published in the scientific literature as</p> <p>9 well as I can.</p> <p>10 Q. Right. You don't start with</p> <p>11 the answer and look for literature to support</p> <p>12 the hypothesized answer only, right?</p> <p>13 MR. FROST: Objection.</p> <p>14 A. Exactly. I do not go to the</p> <p>15 scientific literature only looking for things</p> <p>16 that will support or disprove a particular</p> <p>17 hypothesis. I try to look at the body of</p> <p>18 science as a whole.</p> <p>19 BY MR. SOILEAU:</p> <p>20 Q. Right. And you've discussed</p> <p>21 that process with us some today and we may</p> <p>22 talk about it more, but as you gather the</p> <p>23 available literature, the body of scientific</p> <p>24 evidence, do you at some point in this</p>	<p style="text-align: right;">Page 120</p> <p>1 BY MR. SOILEAU:</p> <p>2 Q. Fair enough.</p> <p>3 Doctor, during your work in</p> <p>4 this project and specifically the generation</p> <p>5 of your expert report, did you at any point</p> <p>6 weigh the evidence on the issue of migration?</p> <p>7 MR. FROST: Objection.</p> <p>8 A. As I said, the scientific</p> <p>9 evidence does not support the hypothesis that</p> <p>10 perineal application of talcum powder can</p> <p>11 cause talcum powder to migrate through the</p> <p>12 female reproductive tract to the ovaries.</p> <p>13 BY MR. SOILEAU:</p> <p>14 Q. Okay. There was really no</p> <p>15 evidence to weigh. Let me back up a step.</p> <p>16 Sometimes when you look at an</p> <p>17 issue and you gather the available scientific</p> <p>18 literature, it is fair to say that at times</p> <p>19 you have competing literature, true?</p> <p>20 A. Again -- again, that's very</p> <p>21 broad.</p> <p>22 Q. Yes, ma'am.</p> <p>23 A. We have to kind of look at a</p> <p>24 body of literature specifically for a</p>
<p style="text-align: right;">Page 119</p> <p>1 process weigh the evidence to see what it</p> <p>2 tells you?</p> <p>3 A. Well, again, we're speaking in</p> <p>4 generalities.</p> <p>5 Q. Yes.</p> <p>6 A. In the case of plausibility, as</p> <p>7 I said, the scientific evidence doesn't</p> <p>8 support the migration theory that perineal</p> <p>9 application can migrate to the ovaries.</p> <p>10 Q. Okay. But you do recognize as</p> <p>11 part of a methodology in the scientific</p> <p>12 process for the analysis of a causal</p> <p>13 relationship the idea of weighing evidence,</p> <p>14 don't you?</p> <p>15 MR. FROST: Objection.</p> <p>16 A. Again, I'm familiar with the</p> <p>17 term "weight of evidence." I'm familiar with</p> <p>18 assessing the body of science. You know, as</p> <p>19 far as what I did here, I assessed the body</p> <p>20 of science as a whole, and as far as weighing</p> <p>21 individual things, that's very general. We'd</p> <p>22 have to probably get more specific into the</p> <p>23 body of science and what we were doing.</p> <p>24 ///</p>	<p style="text-align: right;">Page 121</p> <p>1 topic --</p> <p>2 Q. I understand.</p> <p>3 A. -- and see what the science</p> <p>4 says.</p> <p>5 Q. It was a general question,</p> <p>6 Doctor, and it's simply that when you gather</p> <p>7 the available literature, there are times for</p> <p>8 some issues where there is competing evidence</p> <p>9 on both sides of a question, fair?</p> <p>10 A. Again, you have to look at the</p> <p>11 science as a whole as far as -- as competing.</p> <p>12 You know, again, you're speaking in</p> <p>13 generalities as regards to whether, you know,</p> <p>14 on a given topic science can have different,</p> <p>15 you know, viewpoints or different evidence.</p> <p>16 Q. Sure.</p> <p>17 A. The science is the science.</p> <p>18 You have to just look at the body of science</p> <p>19 as it stands and look at what it shows.</p> <p>20 Q. I mean, that is the art of the</p> <p>21 scientific process, isn't it, gathering the</p> <p>22 evidence and looking at it and seeing what it</p> <p>23 teaches?</p> <p>24 MR. FROST: Objection.</p>

31 (Pages 118 to 121)

Kelly Tuttle, Ph.D.

<p style="text-align: right;">Page 122</p> <p>1 A. I'm sorry, can you repeat the 2 first part of that question? 3 BY MR. SOILEAU: 4 Q. Determination of a causal 5 relationship of a substance like talcum 6 powder is, for you as a toxicologist, 7 different than engineering, isn't it? 8 MR. FROST: Objection. 9 A. I'm sorry. I don't think I 10 understand the question. 11 BY MR. SOILEAU: 12 Q. Okay. I guess in my mind three 13 engineers doing the same engineering 14 calculation will come up with the exact same 15 answer if they've done it appropriately and 16 competently, but that scientists looking at 17 evidence may have different thoughts or 18 opinions even though they look at the same 19 body of evidence. 20 Do you agree with that? 21 MR. FROST: Objection. 22 A. Again, we're speaking in 23 generalities, but, no, if scientists are 24 looking at the same body of science and</p>	<p style="text-align: right;">Page 124</p> <p>1 search. 2 MR. SOILEAU: I started to do 3 that, but I made a pledge to myself 4 that I would not open a computer and 5 be further distracted. I think it was 6 probably a good decision, but I 7 appreciate your help. I don't mind 8 you doing that. Saves us some time. 9 BY MR. SOILEAU: 10 Q. Do you have page 57? 11 A. I do. 12 Q. You say in the second paragraph 13 of Section 11.5, which begins on page 57 of 14 your report, I quote, "First, Dr. Plunkett's 15 migration theory for perineal application 16 would require talc to migrate upwards - 17 against gravity." 18 And I'm stopping in 19 mid-sentence. I just want you ask about 20 the gravity. We can continue in a moment, 21 and I'll acknowledge that the report speaks 22 for itself and continues. 23 But that's the gravity 24 reference that I've seen.</p>
<p style="text-align: right;">Page 123</p> <p>1 applying the same methodology, they should 2 arrive at the same conclusions. 3 BY MR. SOILEAU: 4 Q. Okay. Very well. 5 Is gravity in this context part 6 of the body of evidence that you assembled 7 when you examined the issue of migration of 8 talcum powder through perineal application? 9 MR. FROST: Objection. 10 A. Well, as I said, you need to 11 refer me to where I specifically address 12 gravity. 13 BY MR. SOILEAU: 14 Q. Oh, I'm sorry. 15 A. I recall that I mention it, but 16 as I said, I don't think I used it as a fact. 17 I state that the scientific evidence does not 18 support the migration theory. 19 Q. Sure. I'll point you to it. 20 A. Thank you. 21 MR. FROST: Do you want help? 22 BY MR. SOILEAU: 23 Q. Look at page 57. 24 MR. FROST: I did a word</p>	<p style="text-align: right;">Page 125</p> <p>1 A. Yes, I see it. 2 Q. Do you have any scientific 3 literature to support the idea that gravity 4 is an answer or scientific evidence in 5 opposition to the migration theory, or is 6 this just sort of common sense? 7 A. Well, you know, again, you say 8 that this is just one small portion of looks 9 like at least four on that page, different 10 points I discuss -- 11 Q. That's true. 12 A. -- in relation to the migration 13 theory. 14 Q. But if I ask you about them all 15 at once I'll get in trouble, so I have to 16 break them down and ask one at a time. 17 A. I understand. 18 Q. But that's fine. It's fair 19 that there are several paragraphs and you say 20 first, second, third and fourth on page 57. 21 So I'm on first, and specifically, gravity. 22 What's the role of gravity in 23 all this? 24 A. So again, gravity is just one</p>



Kelly Tuttle, Ph.D.

<p style="text-align: right;">Page 126</p> <p>1 small portion here, and, you know, it is part  2 common sense. I can't provide you with a  3 specific reference in regards to the gravity  4 aspect. That mainly is just one part of the  5 multiple things that I discuss here as far as  6 the scientific literature not supporting the  7 hypothesis that talcum powder can migrate  8 from external perineal application to the  9 ovaries.  10 Q. I see.  11 If I put a straw in this cup of  12 water and the straw is narrow enough in its  13 diameter, will the water always stay at the  14 same level outside the straw and inside the  15 straw or will it be different?  16 MR. FROST: Objection.  17 BY MR. SOILEAU:  18 Q. Or you don't know?  19 A. I don't know.  20 Q. Do you know whether gravity  21 would keep the levels the same?  22 MR. FROST: Objection.  23 A. Again, I -- we can put a straw  24 in the cup of water and perform the</p>	<p style="text-align: right;">Page 128</p> <p>1 gravity is, again as I said, just one part of  2 what I referred to here as far as looking at  3 the scientific evidence and whether it can  4 support the hypothesis of migration or not,  5 and gravity is one of the arguments against  6 the support of an upward migration.  7 BY MR. SOILEAU:  8 Q. I certainly understand it is  9 one and only one of several points you make,  10 but do you think, as we sit here today, the  11 inclusion of gravity is appropriate in this  12 discussion?  13 MR. FROST: Objection.  14 A. Well, again, gravity is a  15 scientific concept and is part of --  16 BY MR. SOILEAU:  17 Q. Sure.  18 A. We have the law of gravity.  19 Q. Newton was right.  20 A. And so I included it here as  21 one of several different things, and as I  22 said, I think there are others who get into  23 the nuances of migration theory much more in  24 depth than I do.</p>
<p style="text-align: right;">Page 127</p> <p>1 experiment.  2 BY MR. SOILEAU:  3 Q. Okay. Is there anything more  4 you can tell me about your reference to  5 gravity or scientific support for the  6 reference to gravity in our discussion of  7 this migration topic?  8 A. Well, as I said, I referred to  9 it very generally in this sentence as part of  10 an overall context regarding the other points  11 that I used to address the migration theory.  12 I know that there are others involved in this  13 litigation that get into this in more detail  14 than I do, so I would have to refer to them.  15 Q. Very well, Doctor.  16 In retrospect, do you think the  17 inclusion of gravity in this discussion of  18 migration of talcum powder products following  19 perineal application is appropriate  20 scientifically?  21 MR. FROST: Objection.  22 A. Well, again, it's one part of  23 the different argument -- different things in  24 examining the scientific evidence. You know,</p>	<p style="text-align: right;">Page 129</p> <p>1 Q. Okay. You stand by the  2 inclusion of gravity. How about that? Is  3 that fair? In your report?  4 A. Yes, I included gravity in  5 there and I do believe, as I said, as part of  6 the scientific evidence and what I address  7 elsewhere in my report it is part of that  8 assessment.  9 Q. You say that there are others.  10 Who are you talking about? Are you talking  11 about other experts?  12 A. Yes, I believe there are other  13 experts involved that get more into the  14 science of the migration theory and discuss  15 those nuances and stuff in more detail than I  16 do.  17 Q. Do you consider yourself to be  18 one of the experts on behalf of Johnson &amp;  19 Johnson possessing appropriate education,  20 background, training and experience to offer  21 opinions on the migration theory?  22 MR. FROST: Objection.  23 A. So as a toxicologist,  24 toxicology is a very broad scientific field</p>

Kelly Tuttle, Ph.D.

<p style="text-align: right;">Page 130</p> <p>1 of study. It encompasses a large number of</p> <p>2 different scientific fields, including</p> <p>3 epidemiology, anatomy and physiology,</p> <p>4 chemistry, molecular biology, cancer biology,</p> <p>5 any number of different fields that all come</p> <p>6 under that umbrella in being able to research</p> <p>7 and understand how chemicals or materials can</p> <p>8 have a potential adverse effect on people or</p> <p>9 the environment or animals.</p> <p>10 BY MR. SOILEAU:</p> <p>11 Q. I've heard that. I appreciate</p> <p>12 that. I didn't cut you off, did I?</p> <p>13 A. Go ahead.</p> <p>14 Q. But do you feel comfortable</p> <p>15 discussing the migration theory within the</p> <p>16 boundaries of your expertise as you view --</p> <p>17 as you view your expertise in this case?</p> <p>18 MR. FROST: Objection.</p> <p>19 A. Well, as I said, I reviewed the</p> <p>20 scientific literature regarding the migration</p> <p>21 theory and whether there's any scientific</p> <p>22 evidence to support the perineal application</p> <p>23 of talcum powder can reach the ovaries --</p> <p>24 ///</p>	<p style="text-align: right;">Page 132</p> <p>1 migration or should we turn to some of these</p> <p>2 others to discuss that issue?</p> <p>3 MR. FROST: Objection.</p> <p>4 BY MR. SOILEAU:</p> <p>5 Q. I just want to know your</p> <p>6 perspective.</p> <p>7 A. No. And as I said, I'll try to</p> <p>8 be a little clearer. Maybe I'm not being</p> <p>9 very clear.</p> <p>10 As part of my training and</p> <p>11 expertise in toxicology, you know, anatomy</p> <p>12 and physiology and molecular biology and</p> <p>13 things like that play -- are an important</p> <p>14 part of the overall science of toxicology.</p> <p>15 So that being said, I have</p> <p>16 reviewed scientific literature regarding</p> <p>17 whether it supports the migration theory or</p> <p>18 not, and I have addressed it in my report and</p> <p>19 summarized it in my report.</p> <p>20 Q. Yes.</p> <p>21 A. I am aware that there are</p> <p>22 others involved in this litigation that, you</p> <p>23 know, focus on the migration theory much more</p> <p>24 specifically than I do and get into more</p>
<p style="text-align: right;">Page 131</p> <p>1 BY MR. SOILEAU:</p> <p>2 Q. Understood.</p> <p>3 A. -- and found no scientific</p> <p>4 evidence to support that.</p> <p>5 And as far as my training and</p> <p>6 expertise, I am -- you know, I review those</p> <p>7 types of studies as part of my ongoing work</p> <p>8 as a toxicologist. I'm not a gynecologist,</p> <p>9 so as I said, there are others involved that</p> <p>10 get into this in more detail than I do, and I</p> <p>11 would have to refer to their work and the</p> <p>12 data that they use in what they provide, but</p> <p>13 ultimately, I would look at the scientific</p> <p>14 literature and generate my own conclusions.</p> <p>15 Q. Right. But, I mean, at home, I</p> <p>16 see my sink and the plumbing and I see water</p> <p>17 and I figure out there's a leak, but if it</p> <p>18 comes to who's going to figure out why it's</p> <p>19 leaking and fixing it, it's going to be a</p> <p>20 plumber; it's not me.</p> <p>21 So I'm just trying to figure</p> <p>22 out, although you've looked at the</p> <p>23 literature, is this migration issue -- are</p> <p>24 you a plumber? Are you able to speak to</p>	<p style="text-align: right;">Page 133</p> <p>1 detail.</p> <p>2 Q. Okay.</p> <p>3 A. And I would certainly refer to</p> <p>4 their work, but I would always ultimately go</p> <p>5 back to the science in forming my own</p> <p>6 opinions.</p> <p>7 Q. I just want to make sure you're</p> <p>8 comfortable speaking with me today about</p> <p>9 migration as an issue in this case, staying</p> <p>10 within your own view of the boundaries or</p> <p>11 limits of your expertise.</p> <p>12 So are you comfortable talking</p> <p>13 about migration with me today?</p> <p>14 MR. FROST: Objection.</p> <p>15 A. As I said, I will certainly --</p> <p>16 I address migration in my report and discuss</p> <p>17 it in my report. I'm happy to discuss what</p> <p>18 I've included in my report if --</p> <p>19 BY MR. SOILEAU:</p> <p>20 Q. Okay.</p> <p>21 A. -- you know, if in the</p> <p>22 toxicological implications and methodologies</p> <p>23 that I use here as far as the scientific</p> <p>24 evidence.</p>

34 (Pages 130 to 133)

Kelly Tuttle, Ph.D.

<p style="text-align: right;">Page 134</p> <p>1 Q. I want to ask one other 2 question about that. You think -- I think 3 you said refer to others, but it almost feels 4 like you mean defer. 5 Do you defer to other experts 6 on the migration? 7 MR. FROST: Objection. 8 BY MR. SOILEAU: 9 Q. Or just you would refer to 10 their opinions too? 11 MR. FROST: Objection. 12 BY MR. SOILEAU: 13 Q. I feel like that was an unclear 14 question. Did you follow it or you want me 15 to kind of resay it? 16 MR. FROST: Objection. 17 A. You can clarify for me, please. 18 BY MR. SOILEAU: 19 Q. You used the word "refer" in 20 talking about others, and as I understand it, 21 other experts for Johnson &amp; Johnson. Would 22 you defer to those other experts on the issue 23 of migration? 24 MR. FROST: Objection.</p>	<p style="text-align: right;">Page 136</p> <p>1 A. Yes, you read that portion 2 correctly. This sentence does continue. 3 Q. Right. As I said before, it 4 does continue. I want to acknowledge that 5 and certainly the report will speak more 6 fully for itself. 7 But I want to focus first on 8 these words, "downward flow of bodily 9 fluids." What role or what significance, if 10 any, do you place in the downward flow of 11 fluids in the context of migration of talcum 12 powder following perineal application? 13 A. Well, again, similar to 14 gravity, this is just one small nu- -- seven 15 or eight words taken out of the whole page on 16 where I look at the -- Dr. Plunkett's theory 17 of particle migration, and it's in 18 conjunction with the statement around 19 gravity. 20 This is, again, just one small 21 portion of it, where we -- and we move on to 22 look at, you know, the scientific literature 23 and scientific evidence that does not support 24 that the particles applied perineally can</p>
<p style="text-align: right;">Page 135</p> <p>1 A. Again, I would refer, and I -- 2 that is correct. I would refer to their 3 reports and things, but I would ultimately go 4 to the science they cite and the basis for 5 their reports in forming my own opinions. 6 BY MR. SOILEAU: 7 Q. Very well. 8 Let's turn back to page 57, 9 where we were a moment ago, still under that 10 second paragraph that begins with the words 11 "First, Dr. Plunkett's migration theory." 12 Let me know when you're there. 13 A. Yes, I'm there. 14 Q. We read through against gravity 15 and stopped. I want to go a little more, and 16 I'll start at the beginning for context. 17 "First, Dr. Plunkett's 18 migration theory for perineal application 19 would require talc to migrate upwards - 20 against gravity and the downward flow of 21 bodily fluids in the female reproductive 22 tract," dash. 23 Did I read that portion 24 correctly?</p>	<p style="text-align: right;">Page 137</p> <p>1 migrate to the ovaries. 2 So again, it's just one part of 3 the evidence that doesn't support the 4 hypothesis. 5 Q. Okay. Is there any scientific 6 evidence or literature cited in your report, 7 Doctor, that supports the relevance of this 8 downward flow of bodily fluids in the context 9 of an analysis of migration? 10 A. I don't believe I cite anything 11 in that particular sentence. You know, I -- 12 again, I didn't get into great detail 13 regarding the downward flow of bodily fluids, 14 the female reproductive tract and the fluids 15 generated there. They have their own defense 16 mechanisms against the introduction of 17 foreign bodies and things like that. 18 Again, I think that others in 19 the -- involved in this litigation get into 20 much more detail regarding that than I do. 21 I'm speaking very generally here before I 22 move into, you know, the complete argument, 23 which I -- as we said, has, I believe, four 24 different addressings here, but looking at</p>

35 (Pages 134 to 137)



Kelly Tuttle, Ph.D.

<p style="text-align: right;">Page 138</p> <p>1 the scientific literature as a whole.</p> <p>2 Q. Do the ovaries have the ability</p> <p>3 to clear foreign particles?</p> <p>4 A. I don't know.</p> <p>5 Q. We're outside of your area now?</p> <p>6 A. Yes, I have not researched</p> <p>7 that. I could -- would certainly be happy to</p> <p>8 research it, but it's not something I</p> <p>9 researched in this litigation.</p> <p>10 Q. Separate from researching it or</p> <p>11 reviewing available literature, is it</p> <p>12 something -- is it a question that you</p> <p>13 believe falls within -- falls properly within</p> <p>14 your expertise, your education, training and</p> <p>15 expertise as a toxicologist?</p> <p>16 MR. FROST: Objection.</p> <p>17 A. Well, again, as I said before,</p> <p>18 you know, toxicology covers a wide range of</p> <p>19 sciences, and the potential effect of adverse</p> <p>20 health effects in the body is definitely in</p> <p>21 the realm of toxicology and study of</p> <p>22 research.</p> <p>23 I did not research ovaries and</p> <p>24 their ability to clear materials. That's not</p>	<p style="text-align: right;">Page 140</p> <p>1 BY MR. SOILEAU:</p> <p>2 Q. Does the respiratory have</p> <p>3 the -- I'm sorry.</p> <p>4 Does the respiratory system</p> <p>5 have the ability to clear foreign particles?</p> <p>6 MR. FROST: Objection.</p> <p>7 A. The respiratory system?</p> <p>8 BY MR. SOILEAU:</p> <p>9 Q. Yes.</p> <p>10 A. Again, that's not something I</p> <p>11 address in my report.</p> <p>12 Q. No, it's not.</p> <p>13 Do you know, as we sit here</p> <p>14 today?</p> <p>15 MR. FROST: Objection.</p> <p>16 A. Generally speaking, and as I</p> <p>17 said, I don't address that specifically in my</p> <p>18 report, but the human body has -- has many</p> <p>19 defense mechanisms for removing materials</p> <p>20 from -- from its -- from the body.</p> <p>21 BY MR. SOILEAU:</p> <p>22 Q. What defense mechanisms do the</p> <p>23 ovaries have?</p> <p>24 MR. FROST: Objection.</p>
<p style="text-align: right;">Page 139</p> <p>1 something I specifically looked at in this</p> <p>2 litigation. It's something that I would</p> <p>3 certainly -- could research and look at the</p> <p>4 scientific evidence, but I didn't do it in</p> <p>5 this case.</p> <p>6 BY MR. SOILEAU:</p> <p>7 Q. Wouldn't you think that would</p> <p>8 be important?</p> <p>9 MR. FROST: Objection.</p> <p>10 A. Well, again, as I state in the</p> <p>11 evidence that we put forward here and I think</p> <p>12 we discussed it earlier, one, scientific</p> <p>13 evidence doesn't support the talcum powder</p> <p>14 applied perineally can migrate to the</p> <p>15 ovaries, but secondarily, we discussed</p> <p>16 earlier that the presence of a chemical or</p> <p>17 particle or something at an organ does not</p> <p>18 necessarily mean that an adverse health</p> <p>19 effect will occur. You need more</p> <p>20 information.</p> <p>21 So as I said, as far as looking</p> <p>22 at the scientific evidence, there's no</p> <p>23 evidence to support that it would migrate to</p> <p>24 begin with.</p>	<p style="text-align: right;">Page 141</p> <p>1 A. Again, I haven't researched</p> <p>2 that specifically to address it. As I said,</p> <p>3 the human body has many defense mechanisms.</p> <p>4 BY MR. SOILEAU:</p> <p>5 Q. Okay. Let me show you the next</p> <p>6 exhibit, which I will mark as Tuttle</p> <p>7 Exhibit 12.</p> <p>8 (Whereupon, Deposition Exhibit</p> <p>9 Tuttle-12, Excerpt from IARC</p> <p>10 Monograph 93, was marked for</p> <p>11 identification.)</p> <p>12 BY MR. SOILEAU:</p> <p>13 Q. Do you recognize, Doctor, the</p> <p>14 exhibit that I have presented to you?</p> <p>15 A. Let me -- I'm trying to keep my</p> <p>16 report in order.</p> <p>17 Q. Sure.</p> <p>18 A. Yes, I do.</p> <p>19 Q. What is this?</p> <p>20 A. This is the 2010 International</p> <p>21 Agency for Research on Cancer monograph that</p> <p>22 includes, among -- talc as well as titanium</p> <p>23 dioxide and carbon black.</p> <p>24 Q. It is cited in your report?</p>

36 (Pages 138 to 141)

Kelly Tuttle, Ph.D.

Page 142	Page 144
<p>1 A. Yes, it is.</p> <p>2 Q. You have a quote at page 57,</p> <p>3 same page we were at earlier. Let me let you</p> <p>4 turn to that. It's still Section 11.5, the</p> <p>5 section that discusses Dr. Plunkett and her,</p> <p>6 as you describe in your report, theory of</p> <p>7 particle migration.</p> <p>8 You say that IARC has concluded</p> <p>9 that the evidence for retrograde transport of</p> <p>10 talc to the ovaries in normal women is weak.</p> <p>11 Do you see that?</p> <p>12 A. Yes, I see where I state that</p> <p>13 in my report.</p> <p>14 Q. All right. And you actually</p> <p>15 quote it. You have quote marks in your</p> <p>16 report for the words, "the evidence for</p> <p>17 retrograde transport of talc to the ovaries</p> <p>18 in normal women is weak," closed quotes,</p> <p>19 right?</p> <p>20 A. Yes.</p> <p>21 Q. And that is taken from the IARC</p> <p>22 Monograph No. 93, which is now Tuttle</p> <p>23 Exhibit 12?</p> <p>24 A. That is the citation I believe.</p>	<p>1 Q. Okay. Now, in your quote, it</p> <p>2 says "the evidence for retrograde transport</p> <p>3 of talc to the ovaries in normal women."</p> <p>4 Why does it say "normal women"</p> <p>5 in the quote you use that you cite and</p> <p>6 reference in your report?</p> <p>7 A. I would need to refer to the</p> <p>8 IARC document and get -- pull out the</p> <p>9 original quote to pull the additional context</p> <p>10 for normal women.</p> <p>11 Q. Do you know as we sit here</p> <p>12 right now without looking at the IARC</p> <p>13 monograph?</p> <p>14 A. Off the top of my head, I can</p> <p>15 assume, but I would prefer not to assume.</p> <p>16 Q. Sure. No, that sounds more of</p> <p>17 a guess than, you know -- an educated guess,</p> <p>18 but a guess, so let's not do that.</p> <p>19 Did you independently review</p> <p>20 any literature on this issue that was</p> <p>21 referenced in or cited by IARC in its</p> <p>22 Monograph 93?</p> <p>23 A. I would need to look at the</p> <p>24 references and compare them, but generally</p>
Page 143	Page 145
<p>1 It says IARC 2010. I can refer to their</p> <p>2 reference list to be specific, but...</p> <p>3 Q. Go ahead and look if you need</p> <p>4 to. Do you have it?</p> <p>5 A. Yes.</p> <p>6 Q. Okay.</p> <p>7 A. And yes, the IARC 2010</p> <p>8 reference is referring to the carbon black,</p> <p>9 titanium dioxide and talc monograph.</p> <p>10 Q. Right. That monograph that is</p> <p>11 IARC Monograph No. 93 has three sections, one</p> <p>12 for carbon black, one for titanium dioxide</p> <p>13 and one for talc, right?</p> <p>14 A. Yes, I believe so. It's a very</p> <p>15 large document, and we have a small subset,</p> <p>16 but I believe those are the three addressed</p> <p>17 specifically. I can't remember if this</p> <p>18 monograph discusses anything as a subset.</p> <p>19 Q. Okay. That's fine. Why don't</p> <p>20 you turn to page 411. Take your time.</p> <p>21 A. Okay.</p> <p>22 Q. Do you see at the top of the</p> <p>23 page it says Talc?</p> <p>24 A. Yes.</p>	<p>1 speaking, that is part of -- you know, when</p> <p>2 looking at some of these documents, you look</p> <p>3 at the data and the science and the reference</p> <p>4 they use to cite for what they state in their</p> <p>5 documents, or in this case, in the monograph.</p> <p>6 Q. All right. I don't have your</p> <p>7 testimony right now. My realtime stopped,</p> <p>8 but let me see if I can understand better.</p> <p>9 There are two scenarios in my mind. One is</p> <p>10 you rely upon IARC and its monograph for the</p> <p>11 statement that is quoted in your report.</p> <p>12 Another possibility is that you</p> <p>13 do not simply rely on the IARC monograph, but</p> <p>14 you independently pull, review and consider</p> <p>15 any literature cited by IARC in its monograph</p> <p>16 to form an independent scientific opinion,</p> <p>17 your own, that is, about what that literature</p> <p>18 might show.</p> <p>19 Which of those two scenarios</p> <p>20 did you employ here as to IARC Monograph 93</p> <p>21 and your discussion of IARC in the context of</p> <p>22 migration?</p> <p>23 MR. FROST: Objection.</p> <p>24 A. So again, the quotations and</p>

37 (Pages 142 to 145)

Kelly Tuttle, Ph.D.

Page 146	Page 148
<p>1 the wording as put forth in my report would</p> <p>2 be directed to the IARC monograph itself.</p> <p>3 Had that been taken from something else, it</p> <p>4 would have been cited to that.</p> <p>5 With that being said, when</p> <p>6 reviewing the IARC monograph or any document</p> <p>7 like it that summarizes a body of science,</p> <p>8 you know, I try to go to the data that is --</p> <p>9 they're reviewing and form my own opinions.</p> <p>10 BY MR. SOILEAU:</p> <p>11 Q. Okay. Let's take a look at the</p> <p>12 paragraph on 411 from which you took your</p> <p>13 quote.</p> <p>14 A. And if I may, before you ask a</p> <p>15 question, we're getting close to the time</p> <p>16 that I'm going to need a break to go nurse.</p> <p>17 Q. Okay. Let's -- if you need to</p> <p>18 stop, stop. I'm going to try to do two</p> <p>19 questions and stop, okay?</p> <p>20 A. Okay.</p> <p>21 Q. Lawyers are bad about</p> <p>22 estimating questions.</p> <p>23 Let's look down here toward the</p> <p>24 bottom of 411. Where it says: On balance,</p>	<p>1 Let's go back to page 411 of</p> <p>2 the monograph, and we had looked at the</p> <p>3 sentence on page 411 that I believe we</p> <p>4 recognized as the source sentence for the</p> <p>5 quote that you have in your report on</p> <p>6 page 57, which we discussed before the break.</p> <p>7 I want to direct you to some additional</p> <p>8 language in that same paragraph.</p> <p>9 Do you see the third sentence</p> <p>10 that begins -- third sentence of the</p> <p>11 paragraph that begins: These have been</p> <p>12 conducted in women who were about to undergo</p> <p>13 gynecological surgery, most of whom had</p> <p>14 diseases or complications of the reproductive</p> <p>15 tract and organs that required surgery.</p> <p>16 Did I read that correctly?</p> <p>17 A. Yes, you read that correctly,</p> <p>18 but as you said, you took the third sentence</p> <p>19 down and it doesn't specify what "these" are.</p> <p>20 I think prior to that it says: Several</p> <p>21 studies have been conducted in women to</p> <p>22 assess potential retrograde movement of</p> <p>23 particles through the reproductive tract to</p> <p>24 the ovaries.</p>
Page 147	Page 149
<p>1 the working group believed that the evidence</p> <p>2 for retrograde transport of talc to the</p> <p>3 ovaries in normal women is weak.</p> <p>4 And I've highlighted it here on</p> <p>5 the page just to try to help you find it.</p> <p>6 I just want to know, is this</p> <p>7 the source statement for the quotation in</p> <p>8 your report?</p> <p>9 A. It appears to be, yes.</p> <p>10 Q. Okay. All right. Then let me</p> <p>11 break a record and stop there and only ask</p> <p>12 one question. We'll take our break now. I</p> <p>13 promised you.</p> <p>14 THE VIDEOGRAPHER: Going off</p> <p>15 the record at 11:34 a.m.</p> <p>16 (Recess taken, 11:34 a.m. to</p> <p>17 12:22 p.m.)</p> <p>18 THE VIDEOGRAPHER: We're back</p> <p>19 on the record at 12:24 p.m.</p> <p>20 BY MR. SOILEAU:</p> <p>21 Q. Good afternoon, Doctor. Are</p> <p>22 you ready to proceed?</p> <p>23 A. Yes, I am.</p> <p>24 Q. Very good.</p>	<p>1 Q. Okay. Let's go back to the</p> <p>2 beginning of the paragraph. That's fair.</p> <p>3 It says, quote, "Perineal</p> <p>4 exposure to cosmetic talc in women is of</p> <p>5 concern because of its possible association</p> <p>6 with ovarian cancer," period.</p> <p>7 And then next, the sentence you</p> <p>8 just referenced: Several studies have been</p> <p>9 conducted in women to assess potential</p> <p>10 retrograde movement of particles through the</p> <p>11 reproductive tract to the ovaries.</p> <p>12 Have I read it correctly thus</p> <p>13 far?</p> <p>14 A. Yes, you have.</p> <p>15 Q. When it says retrograde</p> <p>16 movement, is that, in your view, synonymous</p> <p>17 with the issue of migration that we are</p> <p>18 discussing?</p> <p>19 A. Well, again, it's referring to</p> <p>20 several different studies. As it says, as it</p> <p>21 goes through, it goes -- looking at the</p> <p>22 transport of talc to the ovaries where it</p> <p>23 says, you know, at the end, again, that the</p> <p>24 evidence in normal women is weak, and then</p>

38 (Pages 146 to 149)

Kelly Tuttle, Ph.D.

<p style="text-align: right;">Page 150</p> <p>1 also that evidence in animals with no 2 retrograde transport of talc to the ovaries. 3 Q. Okay. Doctor, that was not my 4 question. My question was simply: When IARC 5 uses the word retrograde movement of 6 particles, do you recognize that as being 7 synonymous for our purposes with the theory 8 of migration of talc particles? 9 A. Well, again, without seeing the 10 specific studies that they're talking about, 11 you know, I don't know what each individual 12 study was looking at in regards to what 13 they're defining as retrograde movement. 14 As I've said before, I -- the 15 scientific evidence doesn't support a 16 transport from external perineal application 17 and so I'd have to look at each individual 18 study that they're referencing here, which 19 they don't cite at the end of this particular 20 sentence. 21 Q. Right. You have not actually 22 looked at any studies in connection with this 23 IARC section, have you? 24 A. Well, as I said before, you</p>	<p style="text-align: right;">Page 152</p> <p>1 reproductive tract to the ovaries. 2 Q. Okay. 3 A. It does not specify from 4 perineal application, doesn't specify from 5 the external application, but merely through 6 the reproductive tract to the ovaries. 7 Q. What are the first two words of 8 the paragraph? 9 A. Of the paragraph, is perineal 10 exposure, but the sentence that we're 11 discussing just says several studies for 12 potential retrograde movement. 13 Q. Okay. Let's continue in the 14 paragraph. Does it go on to say: The 15 findings reported in these studies may be 16 confounded by the various levels of 17 dysfunction in clearance from the female 18 reproductive tract due to underlying 19 pathologies. 20 Did I read that correctly? 21 A. Yes, you read that correctly. 22 Q. What does confounded mean as 23 used in that sentence? Do you know? 24 A. Well, I think we discussed</p>
<p style="text-align: right;">Page 151</p> <p>1 know, there are no particular references 2 listed right here in this paragraph for me to 3 refer to. 4 Q. Right. 5 A. But that being said, as I said 6 previously, I'm looking at the IARC or 7 looking at any, you know, government or 8 agency documents such as this, go through the 9 references and look at the body of science 10 that they refer to in looking at the body of 11 science for scientific evidence. 12 So in order to discuss, you 13 know, retrograde movement as stated here, I 14 would need to go back and look at their 15 references and look at the studies that they 16 are citing. 17 Q. I think I follow you, but I 18 want to ask: Do you know what retrograde 19 movement of particles means as used here in 20 this paragraph from which you have taken your 21 quotation in your report? 22 A. Well, again, I don't have a 23 specific definition. As it says here, it 24 says movement of particles through the</p>	<p style="text-align: right;">Page 153</p> <p>1 confounding generally speaking, but -- and 2 again, we'd have to look at each individual 3 study to see what the individuals say. Just 4 saying that the findings reported in these 5 studies may be confounded may be another term 6 for it -- you know, may be affected or may -- 7 you know, these other issues as far as this 8 IARC says may be involved in the studies, but 9 as I said, we have to look at the individual 10 studies to discuss it specifically. 11 Q. Okay. You said we discussed 12 confounding, but I don't think we did. 13 Do you know what confounding 14 is? 15 MR. FROST: Objection. 16 A. As I said, I mentioned 17 confounding in my report as far as talcum 18 powder and ovarian cancer. In this 19 particular sentence, they mention other 20 things that may be involved in the studies 21 that the IARC is citing, but without looking 22 at those individual studies, I can't discuss, 23 you know, these different things that they 24 state may be confounding or may be involved</p>

Kelly Tuttle, Ph.D.

<p style="text-align: right;">Page 154</p> <p>1 in the studies that they're using.</p> <p>2 BY MR. SOILEAU:</p> <p>3 Q. Okay. I think I follow you. I</p> <p>4 believe you're telling me that without</p> <p>5 looking at the individual studies, you can't</p> <p>6 really be specific about how or why there may</p> <p>7 be confounding. You can't put any meat on</p> <p>8 those bones absent reference to the specific</p> <p>9 study; is that fair?</p> <p>10 A. Right. This is a general</p> <p>11 statement about the studies in general, which</p> <p>12 again, are not cited in this particular</p> <p>13 paragraph, so we can't go to the references,</p> <p>14 which I don't think are in -- included</p> <p>15 here --</p> <p>16 Q. Right.</p> <p>17 A. -- for the basis why they say</p> <p>18 the studies may be confounded and state these</p> <p>19 issues.</p> <p>20 Q. But can you offer a basic</p> <p>21 definition of the term "confounding" as it is</p> <p>22 used, not with reference to any particular</p> <p>23 study, but as a general principle? What does</p> <p>24 it mean that something may confound a study?</p>	<p style="text-align: right;">Page 156</p> <p>1 Q. But I'm not sure if you've told</p> <p>2 me what the word "confound" means in this</p> <p>3 context. Are you able to offer a definition</p> <p>4 of confound?</p> <p>5 A. And any definition I would</p> <p>6 offer right now would be, you know, my</p> <p>7 interpretation or my kind of summation</p> <p>8 without having, you know, what I have in my</p> <p>9 report right in front of me, and I don't want</p> <p>10 to misquote what the scientific definition</p> <p>11 for confounding is.</p> <p>12 Q. Yes, Doctor, I appreciate that.</p> <p>13 Do you have an understanding of</p> <p>14 the principle of confounding within this</p> <p>15 context, the general principle?</p> <p>16 MR. FROST: Objection.</p> <p>17 A. Well, again, we're speaking in</p> <p>18 generalities, and without looking at these</p> <p>19 studies, confounding may mean something</p> <p>20 slightly different depending on the study and</p> <p>21 what the authors are doing as far as they</p> <p>22 state here, assessing potential retrograde</p> <p>23 movement of particles.</p> <p>24 ///</p>
<p style="text-align: right;">Page 155</p> <p>1 MR. FROST: Objection.</p> <p>2 BY MR. SOILEAU:</p> <p>3 Q. Do you know?</p> <p>4 A. Sorry, I'm trying -- I believe</p> <p>5 I talk a little bit about confounding in the</p> <p>6 causation section of my report, especially in</p> <p>7 regards to specific causation, when looking</p> <p>8 at confounding factors.</p> <p>9 Q. Right. You understand here</p> <p>10 we're really focused on general causation, or</p> <p>11 do you understand that in this -- this</p> <p>12 Daubert proceeding that is referenced in your</p> <p>13 invoice as the Daubert challenge process?</p> <p>14 You understand we're really</p> <p>15 looking at general causation as opposed to a</p> <p>16 particular woman?</p> <p>17 A. Well, again, it is my</p> <p>18 understanding that we're looking at the</p> <p>19 scientific evidence to establish whether</p> <p>20 there is a causal association, which again,</p> <p>21 would be general causation --</p> <p>22 Q. Right.</p> <p>23 A. -- as far as what the</p> <p>24 scientific evidence supports.</p>	<p style="text-align: right;">Page 157</p> <p>1 BY MR. SOILEAU:</p> <p>2 Q. You have used the word</p> <p>3 "confounded" before in your own writings,</p> <p>4 haven't you?</p> <p>5 A. Yes, I have.</p> <p>6 Q. When you use the word</p> <p>7 "confounded" in your own writings, what do</p> <p>8 you mean by that word?</p> <p>9 A. Well, again, it would depend on</p> <p>10 the context. I'd have to, you know, as I</p> <p>11 said, I've certainly used it on numerous</p> <p>12 occasions, and -- but I would need to see the</p> <p>13 context of how I was using it to be able to</p> <p>14 accurately describe what I meant by it when I</p> <p>15 used it in a sentence.</p> <p>16 Q. Let's do this. I'm going to</p> <p>17 show you another exhibit. I'll mark this as</p> <p>18 Tuttle Exhibit 13.</p> <p>19 (Whereupon, Deposition Exhibit</p> <p>20 Tuttle-13, Egli and Newton</p> <p>21 Publication, was marked for</p> <p>22 identification.)</p> <p>23 BY MR. SOILEAU:</p> <p>24 Q. Perhaps it will save time.</p>

40 (Pages 154 to 157)



Kelly Tuttle, Ph.D.

<p style="text-align: right;">Page 158</p> <p>1 Could you -- I think you're going to. Go</p> <p>2 ahead and turn to the references that begin</p> <p>3 at page 72, I believe, of your report, and</p> <p>4 conveniently, it's alphabetized, so if you</p> <p>5 can go to the Es and see if this report by</p> <p>6 G.E. Egli, E-G-L-I, Dr. Egli is one of the</p> <p>7 reference materials that you considered in</p> <p>8 this matter?</p> <p>9 A. It is not one of the references</p> <p>10 that I cite.</p> <p>11 Q. Is it by chance familiar to you</p> <p>12 generally for whatever reason?</p> <p>13 A. If I may, I'm just briefly</p> <p>14 looking at it.</p> <p>15 Q. Let me direct you -- and you</p> <p>16 may do that, but I'm going to direct you to</p> <p>17 page 153, and there's some language under</p> <p>18 Discussion that says at page 153 of Tuttle</p> <p>19 Exhibit 13, the Egli paper, that this study</p> <p>20 indicates that in two cases under the</p> <p>21 conditions outlined, inert carbon particles</p> <p>22 placed in the posterior fornix of the vagina</p> <p>23 were found 28 and 34 minutes later in both</p> <p>24 tubes.</p>	<p style="text-align: right;">Page 160</p> <p>1 paper. I think Egli was 1961. That was</p> <p>2 Tuttle Exhibit 13. So Exhibit 14 is</p> <p>3 Henderson 1971.</p> <p>4 Can you look and see if that is</p> <p>5 referenced among the materials that you</p> <p>6 reviewed in your consideration of the</p> <p>7 scientific evidence and literature in this</p> <p>8 matter?</p> <p>9 A. No, it is not.</p> <p>10 Q. Could you turn to page 268.</p> <p>11 A. If you don't mind, since this</p> <p>12 is something -- you know, that, as with the</p> <p>13 Egli study, that I have not seen, if you can</p> <p>14 give me just a moment to familiarize myself</p> <p>15 with it somewhat.</p> <p>16 Q. Sure. I tell you what I'm</p> <p>17 going to do. I'm going to show you what I'm</p> <p>18 interested in for reference without asking</p> <p>19 you any questions about it, and then you can</p> <p>20 take some time if you need to to look at this</p> <p>21 paper, okay?</p> <p>22 A. Thank you.</p> <p>23 Q. So I'm looking at -- on page 3</p> <p>24 of 7, which is 268, I've highlighted some</p>
<p style="text-align: right;">Page 159</p> <p>1 Do you see that?</p> <p>2 A. Yes, I see that. I'm not</p> <p>3 familiar with this article, but I note that</p> <p>4 it's dealing with, as you said, inert carbon</p> <p>5 particles and dealing with a vaginal</p> <p>6 application as opposed to a perineal.</p> <p>7 Q. Okay. Do you know what the</p> <p>8 posterior fornix of the vagina is?</p> <p>9 A. Not specifically, no, I don't</p> <p>10 know.</p> <p>11 Q. Okay. Are you familiar with</p> <p>12 carbon particles generally as a substance or</p> <p>13 agent?</p> <p>14 A. Yes, generally.</p> <p>15 Q. Okay. Let me show you an</p> <p>16 additional paper. I'll mark this as Tuttle</p> <p>17 Exhibit 14.</p> <p>18 (Whereupon, Deposition Exhibit</p> <p>19 Tuttle-14, 1971 Henderson et al</p> <p>20 Publication, was marked for</p> <p>21 identification.)</p> <p>22 BY MR. SOILEAU:</p> <p>23 Q. Tuttle Exhibit 14, the lead</p> <p>24 author is W.J. Henderson. It is a 1971</p>	<p style="text-align: right;">Page 161</p> <p>1 language here that says: The talc particles</p> <p>2 were found deep within the tumor tissue.</p> <p>3 Talc particles were also found embedded</p> <p>4 within tumors of the cervix.</p> <p>5 And second -- there are a</p> <p>6 number of photographs or images, perhaps is a</p> <p>7 better word, included in this paper. When</p> <p>8 you get into the discussion on page 271, the</p> <p>9 language that appears on the second column:</p> <p>10 There was good evidence for the presence of</p> <p>11 talc, often indistinguishable from</p> <p>12 anthophyllite asbestos within the ovarian</p> <p>13 tissue.</p> <p>14 It also says, after the</p> <p>15 parenthetical: The talc particles were found</p> <p>16 localized deep within tumor tissues. And it</p> <p>17 continues.</p> <p>18 Those are the two sections that</p> <p>19 I'm focused on in my review of this</p> <p>20 scientific paper.</p> <p>21 A. Okay. And I apologize, you</p> <p>22 were moving a little too fast for me. Can I</p> <p>23 get you to direct me to where they are on the</p> <p>24 page on 268 and -- oh.</p>

41 (Pages 158 to 161)



Kelly Tuttle, Ph.D.

<p style="text-align: right;">Page 162</p> <p>1 Q. I'm going to loan you my 2 highlighted copy of Tuttle Exhibit 14. 3 A. Thank you. 4 (Document review.) 5 BY MR. SOILEAU: 6 Q. As you're reviewing that paper, 7 is it at all familiar to you? 8 A. As I said, no, I don't cite it 9 in my report. 10 Q. Okay. I understand that. And 11 your review thus far has not caused it -- it 12 doesn't ring a bell. How about that? 13 A. Correct. 14 Q. I note in the summary of the 15 Henderson '71 paper it says: An 16 extraction-replication technique was used to 17 examine tissue from patients with ovarian and 18 cervical tumors. In both conditions talc 19 particles were found deeply embedded within 20 the tumor tissue. The close association of 21 talc to the asbestos group of minerals is of 22 interest. 23 That's on the first page. 24 Is there anything you wanted to</p>	<p style="text-align: right;">Page 164</p> <p>1 A. Yes, and we said "and further 2 investigations are obviously required." 3 Q. Very well. 4 Let me show you a document that 5 I'll mark as Tuttle Exhibit 15. This is a 6 paper by Venter from 1979. And tell me first 7 if it is included among your reference 8 materials that list the studies and 9 scientific evidence that you considered 10 following your gathering process. 11 (Whereupon, Deposition Exhibit 12 Tuttle-15, 1979 Venter et al 13 Publication, was marked for 14 identification.) 15 A. No, it is not. 16 BY MR. SOILEAU: 17 Q. Okay. I'm looking here on the 18 first page. There's a reference to 19 migration. It says: Such migration could 20 well explain the etiological role of chemical 21 substances in certain gynecological diseases. 22 Do you see that? The first 23 page, second column. 24 A. Oh, okay.</p>
<p style="text-align: right;">Page 163</p> <p>1 add about this paper right now? I'm going to 2 move to another one. 3 A. Certainly. The article appears 4 to be the development of a method regarding 5 the study of foreign particles within 6 tissues, and I would not in -- after reading 7 the snippets that you pulled from page 268 8 and 271, that the overall premise of this 9 study was the development of a method, and 10 they actually conclude at the end that 11 although it is impossible to incriminate talc 12 as a primary cause of carcinomatous changes 13 within either the cervix or the ovary on the 14 preliminary observations described here, and 15 then they go on to say that further 16 investigations are obviously required. 17 Q. Well, you just left out 18 something, didn't you? 19 A. If you like, I can read it in 20 its entirety. 21 Q. Didn't you omit the words: The 22 possibility that talc may be related to other 23 predisposing factors should not be 24 disregarded?</p>	<p style="text-align: right;">Page 165</p> <p>1 Q. Third sentence. The prior 2 sentence says: Will a chemical substance 3 deposited in the vagina later appear in the 4 peritoneal cavity. 5 A. Yes, I see it. 6 Q. Okay. Let me show you another 7 paper that I will mark as Tuttle Exhibit 16. 8 A. Well, if I may -- 9 Q. Sure. You want to add 10 something about that one? 11 A. -- I'm not familiar with this 12 article, so I don't know what the premise is. 13 I notice that what you said was deposited in 14 the vagina, which is, again, different from 15 perineal application is what we were 16 discussing, and -- 17 Q. Okay. 18 A. -- in this particular case. So 19 I just wanted to point out that, again, this 20 doesn't seem to be -- I haven't had time to 21 review it or look at this report and see what 22 the actual objectives of it were. 23 Q. I understand. And I want to 24 allow you the opportunity to offer those</p>

Kelly Tuttle, Ph.D.

<p style="text-align: right;">Page 166</p> <p>1 comments. I understand that you've not 2 reviewed it. 3 Really what I'm trying to do is 4 verify that these studies that I have here 5 are not studies that is -- that these studies 6 that I have here are studies you have not 7 considered in offering the opinions that you 8 offer today. 9 Let me show you -- 10 MR. FROST: Objection. 11 BY MR. SOILEAU: 12 Q. -- what I've marked as Tuttle 13 Exhibit 16. 14 (Whereupon, Deposition Exhibit 15 Tuttle-16, 1986 Henderson et al 16 Publication, was marked for 17 identification.) 18 BY MR. SOILEAU: 19 Q. When we say perineal, I mean, 20 perineum, perineal -- perineal means 21 involving the perineum; is that right? 22 A. When we refer to perineal 23 application, generally we're referring to the 24 application of talcum powder to the exterior</p>	<p style="text-align: right;">Page 168</p> <p>1 with your work in this matter? 2 A. Again, it is not cited in my 3 report. 4 Q. Do you see in this 1986 paper 5 by Henderson and others, which we've marked 6 as Tuttle Exhibit 16, on the first page, 7 second paragraph of the introduction: Direct 8 communication between the external 9 environment and the peritoneal cavity exists 10 in the female via her genital tract. 11 Do you see that statement, 12 first of all? 13 A. Yes, I see that statement, but 14 it's included in the introduction with no 15 citations for it, so I don't know where 16 they're basing -- you know, what that is 17 based on. 18 Q. Okay. Do you agree or disagree 19 with that statement as I read it? 20 MR. FROST: Objection. 21 A. As I just said, it's in the 22 introduction. There's no reference cited to 23 it. I don't know the basis for this 24 statement, so I can't agree or disagree, and,</p>
<p style="text-align: right;">Page 167</p> <p>1 genitalia. 2 Q. The perineum? 3 A. Yes. 4 Q. Does it include the opening of 5 the vagina? 6 A. It includes the external 7 opening. 8 Q. Right. Okay. I just want to 9 make sure that that's clear, that we are 10 talking about an area that includes the 11 external opening of the vagina. 12 MR. FROST: Objection. 13 BY MR. SOILEAU: 14 Q. Is that right, to your 15 understanding of the perineum? 16 A. Again, as I said, it involves 17 the external genitalia of the female body. 18 Q. Including the vagina? 19 A. Yes, including the vagina. 20 Q. Okay. Let's turn to 21 Exhibit 16, the Henderson paper from 1986. 22 Could you tell me if that is included among 23 the materials, evidence, scientific 24 literature that you considered in connection</p>	<p style="text-align: right;">Page 169</p> <p>1 you know, without reading this, having a 2 moment to read this article or any of the 3 articles that we've discussed, I -- you know, 4 I can't discuss it in detail other than to 5 say a cursory glance of all of these don't 6 look at, as we were just saying, the perineal 7 application of talc particles, but merely 8 variations of either particles that are not 9 talc or scenarios where either it's a method 10 development and is not looking at how -- talc 11 migration, period, other than just looking at 12 a method development, and, you know, a lot of 13 these are looking at vaginal introduction or 14 something that doesn't -- that already kind 15 of takes one step past the external 16 application. 17 BY MR. SOILEAU: 18 Q. Okay. Do any of these papers 19 that I have shown you thus far impact or move 20 your opinion on migration? 21 MR. FROST: Objection. Sorry, 22 I had food in my mouth. Objection. 23 MR. SOILEAU: Noted. We'll 24 accept that.</p>

43 (Pages 166 to 169)

Kelly Tuttle, Ph.D.

<p style="text-align: right;">Page 170</p> <p>1 A. As I said before, I haven't had 2 an opportunity to read these, look at their 3 data, their scientific evidence. Some of 4 these, I can't -- you know, I don't know what 5 the purpose of these studies are or what they 6 were being used for. 7 BY MR. SOILEAU: 8 Q. Very well. 9 Let me show you another 10 article. This one I've marked as Tuttle 11 Exhibit 17. It is by Kissler, K-I-S-S-L-E-R. 12 (Whereupon, Deposition Exhibit 13 Tuttle-17, 2004 Kissler et al 14 Publication, was marked for 15 identification.) 16 BY MR. SOILEAU: 17 Q. Is this one included among the 18 materials that you have reviewed, Doctor? 19 A. No, it is not. 20 Q. Look at the first page under 21 the abstract, really the last sentence. It 22 says, quote, "Directed uterine contractility 23 and intact uterotubal transport function are 24 considered necessary for intact sperm</p>	<p style="text-align: right;">Page 172</p> <p>1 MR. FROST: Objection. 2 A. Again, I -- no, I don't know. 3 I haven't -- I haven't researched that. 4 BY MR. SOILEAU: 5 Q. All right. Let me show you 6 what I will mark as Tuttle Exhibit 18. 7 (Whereupon, Deposition Exhibit 8 Tuttle-18, 2004 Sj?sten et al 9 Publication, was marked for 10 identification.) 11 BY MR. SOILEAU: 12 Q. It is a 2004 paper, the lead 13 author is Sj?sten, I think is the 14 pronunciation. It is spelled S-J-O-S-T-E-N; 15 the O has the double dots over it. We've 16 exhausted my knowledge of that language. I 17 believe it's the correct pronunciation. 18 Is this one included among the 19 materials that you've reviewed, the one that 20 I've marked as Tuttle Exhibit 18? 21 A. No, it is not. 22 Q. Look at the conclusion on 23 page 1 of Tuttle Exhibit 18, the Sj?sten 24 article. Conclusions: This study has</p>
<p style="text-align: right;">Page 171</p> <p>1 transport mainly due to the side bearing the 2 dominant follicle to maximize fertility." 3 Do you see that sentence? 4 A. Yes, I see that, and this 5 appears to, again, without having an 6 opportunity to review it, this appears to be 7 something that examines sperm transport, 8 and... 9 Q. Right. 10 A. And again, uterine 11 contractility, but nothing about perineal 12 application of talcum powder or talc particle 13 migration from the external genitalia. 14 Q. Okay. What is directed uterine 15 contractility, if you know? 16 MR. FROST: Objection. 17 A. I haven't read the article. I 18 don't know. 19 BY MR. SOILEAU: 20 Q. Okay. And I'm -- to be clear, 21 to be fair, I'm not asking you what meaning 22 it has in the article. I'm asking you 23 generally, what is directed uterine 24 contractility? Do you know?</p>	<p style="text-align: right;">Page 173</p> <p>1 pointed out a retrograde migration of starch 2 also in humans after a gynecological 3 examination with powdered gloves. 4 Consequently, powder or other potentially 5 harmful substance that can migrate from the 6 vagina should be avoided. 7 Did I read that correctly? 8 MR. FROST: Objection. 9 A. Yes, you read that correctly, 10 but again, with -- I haven't had a chance to 11 review this. It appears, as you said, a 12 gynecological examination, which would be, 13 again -- it states it in your sentence, from 14 the vagina as opposed to from the external 15 genitalia, to the ovaries. And as you 16 mentioned, it's looking at starch and not 17 talcum powder. 18 But I would need some time to 19 review this briefly to discuss it. 20 BY MR. SOILEAU: 21 Q. Do you recognize the journal 22 that this article was apparently published in 23 in 2004? 24 A. Not specifically, no.</p>

44 (Pages 170 to 173)

Kelly Tuttle, Ph.D.

Page 174	Page 176
<p>1 Q. Okay. It's Human Reproduction. 2 That's not familiar to you, is it? 3 A. Not specifically, no. 4 Q. And, I'm sorry, you told me 5 this was not included among the materials you 6 reviewed, right? 7 MR. FROST: Objection. 8 A. That's correct. 9 BY MR. SOILEAU: 10 Q. I'm sorry if I asked that 11 before. 12 Let me show you an additional 13 study. I'll mark this one as Tuttle 14 Exhibit 19. 15 (Whereupon, Deposition Exhibit 16 Tuttle-19, 2019 McDonald et al 17 Publication, was marked for 18 identification.) 19 BY MR. SOILEAU: 20 Q. This is a 2019 paper, the lead 21 author is McDonald. It was published, I 22 believe, in Ultrastructural Pathology. 23 Is this paper included in the 24 materials that you reviewed and considered in</p>	<p>1 perineal application of talc and the 2 migration of talc into the upper genital 3 tract through the fallopian tubes eventually 4 and ultimately reaching the ovaries, right? 5 A. So again, you haven't given me 6 an opportunity to read this article in its 7 entirety, but I notice that after it makes 8 that statement it cites two different 9 residences, and if we go back and look -- 10 Q. Sure. 11 A. -- it cites number 11, which is 12 a Cramer study, which I don't believe we've 13 discussed yet, but it's -- number 16 is 14 the -- I believe it's the Henderson study we 15 briefly touched on. 16 Q. Yes. 17 A. And again, none of the studies 18 that you've shown me, I haven't had a chance 19 to review them in detail, but none of them 20 look at -- as this statement implies, talc 21 when applied to perineum, to the external 22 genitalia, and, you know, as it says here, is 23 believed. 24 Q. Okay.</p>
Page 175	Page 177
<p>1 forming the opinions that you offer today, 2 Doctor? 3 A. No, it is not. 4 Q. All right. If you would look 5 to page 12 under Discussion, the second 6 paragraph, where it states: Talc, when 7 applied to the perineum, is believed to 8 migrate to the upper genital tract, passing 9 through the open tract to the fallopian tubes 10 and eventually reaching the ovaries. End the 11 quote. 12 Let me let you find that. I'm 13 showing it on the screen, highlighted, but 14 again, page 12, second paragraph of 15 Discussion of Tuttle Exhibit 19. 16 Now, this statement is on 17 point, isn't it? 18 MR. FROST: Objection. 19 BY MR. SOILEAU: 20 Q. Well, this statement -- let me 21 be more specific. That's probably fair. 22 This statement is talking about 23 talc and it's talking about talc applied to 24 the perineum and it's talking about the</p>	<p>1 A. So again, we're taking one 2 sentence out of context, and these are all 3 articles that I haven't had a chance to read 4 in depth or look at the data or the 5 information or even the objectives of these 6 articles herein. 7 But none of them as stated have 8 looked at the external perineal application 9 of talcum powder and its potential or 10 hypothetical migration. 11 Q. What do you mean you have not 12 had a chance? "I've not had a chance to 13 read." Why not? 14 A. Well, as I'm saying, as you've 15 put them in front of me, you haven't given me 16 an opportunity to look at them. 17 Q. Oh. 18 A. They weren't cited in my 19 report. 20 Q. I understand. But there's no 21 reason to think that they would not have been 22 available to you prior to today, correct? 23 MR. FROST: Objection. 24 A. Well, as I said in cursory --</p>

45 (Pages 174 to 177)



Kelly Tuttle, Ph.D.

<p style="text-align: right;">Page 178</p> <p>1 as we've gone through these, there have --</p> <p>2 without having a chance to actually look at</p> <p>3 them in detail, I can't speak to it</p> <p>4 specifically. We can go through each one,</p> <p>5 I'd be happy to.</p> <p>6 In the case of the others not</p> <p>7 previously -- sorry, looking at the others</p> <p>8 we've previously discussed, again, none of</p> <p>9 them looked at external perineal application</p> <p>10 and talcum powder or they looked at particles</p> <p>11 that were not talcum powder, or in the case</p> <p>12 of some of them, they were just method</p> <p>13 developments and things. But I would need to</p> <p>14 be able to look at them specifically.</p> <p>15 And then in the case of this</p> <p>16 McDonald one, actually, this one would not</p> <p>17 have been available via PubMed search judging</p> <p>18 by the article history on the front page</p> <p>19 saying that it was accepted in March of this</p> <p>20 year.</p> <p>21 So again, I'd need to be able</p> <p>22 to read it and review it to discuss it.</p> <p>23 BY MR. SOILEAU:</p> <p>24 Q. Can we agree that the McDonald</p>	<p style="text-align: right;">Page 180</p> <p>1 That sentence, whether you</p> <p>2 agree with it or disagree -- and I understand</p> <p>3 you've not seen this paper before today, but</p> <p>4 that topic sentence puts it squarely on point</p> <p>5 for the discussion we're having right now,</p> <p>6 doesn't it, Doctor?</p> <p>7 MR. FROST: Objection.</p> <p>8 A. Well, again, you've taken one</p> <p>9 sentence out of the second paragraph of the</p> <p>10 discussion -- of a discussion of an article</p> <p>11 that goes on for over two pages. It cites</p> <p>12 two references, neither of which support --</p> <p>13 or well, excuse me, the one that we've looked</p> <p>14 at so far does not support the statement, and</p> <p>15 as it says, it just is believed.</p> <p>16 So without being able to look</p> <p>17 at the entire document, you know, no, I can't</p> <p>18 speak to whether it is applicable to the</p> <p>19 external perineal application of talcum</p> <p>20 powder and migration or not.</p> <p>21 BY MR. SOILEAU:</p> <p>22 Q. Okay. Let's do this for a</p> <p>23 moment. Let's go back to Tuttle Exhibit 12.</p> <p>24 It's the excerpt from the IARC Monograph 93</p>
<p style="text-align: right;">Page 179</p> <p>1 paper does address talc, application of talc</p> <p>2 to the perineum and migration of talc</p> <p>3 following perineal application to the</p> <p>4 ovaries?</p> <p>5 MR. FROST: Objection.</p> <p>6 BY MR. SOILEAU:</p> <p>7 Q. That's what this is talking</p> <p>8 about, isn't it?</p> <p>9 MR. FROST: Objection.</p> <p>10 A. Again, I haven't had a chance</p> <p>11 to read anything on it yet except for the one</p> <p>12 sentence that we pulled that was referenced</p> <p>13 to two other publications, which as we were</p> <p>14 discussing, don't look at perineal</p> <p>15 application. I'm happy to take a minute to</p> <p>16 look at this so we can discuss it.</p> <p>17 BY MR. SOILEAU:</p> <p>18 Q. I just really wanted to know</p> <p>19 that this sentence is -- this sentence I'm</p> <p>20 quoting from the McDonald paper, which is</p> <p>21 Tuttle Exhibit 19, is talking about the thing</p> <p>22 you and I are talking about right now,</p> <p>23 migration of talc to the ovaries following</p> <p>24 perineal application.</p>	<p style="text-align: right;">Page 181</p> <p>1 that you have before you. And by the way,</p> <p>2 you're correct, this isn't the entire</p> <p>3 monograph. I keep calling it the monograph,</p> <p>4 and I think you clarified that at some point,</p> <p>5 and I want to sort of stand in agreement with</p> <p>6 you. This is a section of that monograph.</p> <p>7 But it starts with the</p> <p>8 discussion of mechanistic and other relevant</p> <p>9 data on talc and continues, beginning at</p> <p>10 page 391, for our exhibit, so...</p> <p>11 I want you to turn to page 392.</p> <p>12 Do you recall when we were looking at the</p> <p>13 paragraph from which you took the quote that</p> <p>14 you used in your report, that is the IARC</p> <p>15 language that you quoted and included in your</p> <p>16 report, you made the point that they didn't</p> <p>17 show any studies there?</p> <p>18 A. Yes, that --</p> <p>19 Q. Remember on page 411?</p> <p>20 A. Yes, that's correct.</p> <p>21 Q. Okay. But now if we go back to</p> <p>22 page 392, they are talking about studies</p> <p>23 here, aren't they?</p> <p>24 A. Yes, generally speaking, I see</p>

Kelly Tuttle, Ph.D.

Page 182	Page 184
<p>1 several citations throughout the text.</p> <p>2 Q. Right. And if you go to the</p> <p>3 last paragraph on page 392, isn't it true</p> <p>4 that the first study referenced in this IARC</p> <p>5 monograph is Egli and Newton from 1961?</p> <p>6 A. Yes, it is.</p> <p>7 Q. And isn't that the same paper</p> <p>8 that I presented to you earlier, Egli and</p> <p>9 Newton, 1961, which is now Tuttle Exhibit 13?</p> <p>10 A. Well, I would normally refer to</p> <p>11 the references of the monograph to confirm</p> <p>12 that. As I think I've said before, I don't</p> <p>13 know if Egli published anything else in that</p> <p>14 year.</p> <p>15 Q. Well, read what it says. Egli</p> <p>16 and Newton, 1961 found that inert carbon</p> <p>17 particles deposited in the vagina in two of</p> <p>18 three patients traveled to the fallopian</p> <p>19 tubes in about 30 minutes.</p> <p>20 Isn't that consistent with the</p> <p>21 Egli paper that we reviewed and that is</p> <p>22 Tuttle Exhibit 13?</p> <p>23 MR. FROST: Objection.</p> <p>24 A. Well, again, I wasn't -- I</p>	<p>1 can't we?</p> <p>2 A. That's correct, I did not cite</p> <p>3 them in my report.</p> <p>4 Q. So doesn't that tell us that</p> <p>5 you didn't look at an Egli and Newton paper</p> <p>6 from 1961?</p> <p>7 A. Well, again, as I said, when</p> <p>8 looking at the -- what limited information</p> <p>9 I'm given, you know, this -- the Egli and</p> <p>10 Newton report, one, does not look at talc</p> <p>11 particles; two, does not like at perineal</p> <p>12 application; and three, in this particular</p> <p>13 statement as put forth by IARC, doesn't look</p> <p>14 at the ovaries but at the fallopian tubes.</p> <p>15 So I am again, you know, not</p> <p>16 seeing anything based on what I've been able</p> <p>17 to review for this article that it would</p> <p>18 support the migration theory of perineal</p> <p>19 application of talcum powder and migration to</p> <p>20 the ovaries. So I don't see why I would have</p> <p>21 found it or cited it in my report.</p> <p>22 Q. Okay, Doctor. But, no, that's</p> <p>23 not my point. My point -- let me clarify --</p> <p>24 is you have used this monograph, Volume 93,</p>
Page 183	Page 185
<p>1 didn't get a chance to sit here and review</p> <p>2 the Egli paper. I do know that it looked</p> <p>3 at -- you know, is based on the title and</p> <p>4 what little chance I did get to look at it,</p> <p>5 it does involve inert carbon particles that</p> <p>6 were deposited in the vagina and looking at</p> <p>7 the fallopian tubes, but...</p> <p>8 BY MR. SOILEAU:</p> <p>9 Q. Well, let's do this. When I</p> <p>10 showed you the Egli paper from 1961 that we</p> <p>11 marked as Tuttle Exhibit 13, you reviewed</p> <p>12 your reference materials at my request,</p> <p>13 didn't you?</p> <p>14 A. Yes, I did.</p> <p>15 Q. And when you did that, you</p> <p>16 found no Egli paper from 1961, correct?</p> <p>17 A. That's correct. I didn't cite</p> <p>18 it in my report.</p> <p>19 Q. That's correct.</p> <p>20 So regardless of how many</p> <p>21 papers Dr. Egli and Newton -- Drs. Egli and</p> <p>22 Newton published in 1961, if it's one or more</p> <p>23 than one, you didn't cite any of them in your</p> <p>24 reference materials. We can agree on that,</p>	<p>1 and specifically some words on page 411 that</p> <p>2 you quote in your report to say that the</p> <p>3 working group believed that the evidence for</p> <p>4 retrograde transport of talc to the ovaries</p> <p>5 in normal women is weak.</p> <p>6 You drew upon that and quoted</p> <p>7 it in your report, didn't you?</p> <p>8 A. Yes, I quoted that in my</p> <p>9 report.</p> <p>10 Q. Right. And I think we looked</p> <p>11 at it. It's at page 57 of your report,</p> <p>12 correct?</p> <p>13 A. Yes, it's on page 57.</p> <p>14 Q. And that Section 11.5 of your</p> <p>15 report, one of the sections that is quite</p> <p>16 critical of Dr. Plunkett, fair?</p> <p>17 MR. FROST: Objection.</p> <p>18 A. I'm not critical of</p> <p>19 Dr. Plunkett, merely of the methodology</p> <p>20 and -- the methodology used in Dr. Plunkett's</p> <p>21 report. And as I -- you know, as we've said</p> <p>22 before, this particular page has about four</p> <p>23 different topics that I address in addressing</p> <p>24 the theory of particle migration from the</p>

47 (Pages 182 to 185)



Kelly Tuttle, Ph.D.

Page 186	Page 188
<p>1 genital area to the ovaries. 2 BY MR. SOILEAU: 3 Q. Well, you did say in the topic 4 sentence or title to Section 11.5 that 5 Dr. Plunkett's theory of particle migration 6 was severely flawed, didn't you? 7 MR. FROST: Objection. 8 A. As I -- I think I've said 9 before, I state that the theory has not been 10 established in the scientific literature and 11 is severely flawed. 12 BY MR. SOILEAU: 13 Q. You did use the words "severely 14 flawed" in referring to Dr. Plunkett and her 15 discussion of particle migration, didn't you? 16 Did you use those word, "severely flawed"? 17 A. I used severely flawed, but not 18 in reference to Dr. Plunkett, but rather to 19 the scientific -- you know, the theory of 20 particle migration. 21 Q. Okay. Very well. 22 But my point is: In 23 criticizing Dr. Plunkett, you quoted IARC, 24 correct?</p>	<p>1 Newton study, referenced by IARC in this 2 discussion, fair? 3 A. In that particular paragraph. 4 There are paragraphs before that that again 5 cite several other articles, and there are 6 other articles cited afterwards. We've only 7 looked at the handful that you've presented 8 to me that I haven't cited. We haven't gone 9 through all the references in the IARC 10 monograph to see which ones I cited and which 11 ones I did not. 12 Q. Sure. That's fine. And my 13 time is a bit limited, but we can agree that 14 we know that this first study at the 15 beginning of this paragraph, Egli and Newton, 16 is cited by IARC, correct? 17 A. Yes, it is cited by IARC. 18 Q. And you did not look at it, did 19 you? 20 MR. FROST: Objection. 21 A. Again, I did not cite it in my 22 report. As I said previously, when looking 23 at the IARC documents and looking at any of 24 these documents, you look at the data and the</p>
Page 187	Page 189
<p>1 MR. FROST: Objection. 2 BY MR. SOILEAU: 3 Q. Second paragraph, page 57 of 4 your report, Section 11.5. You said: 5 Indeed, IARC has concluded. 6 And then we get back to the 7 quote. 8 A. Yes, I quote IARC there in that 9 first -- that second paragraph under the 10 heading 11.5. But again, I'm not critical of 11 Dr. Plunkett, but merely the methodologies 12 used. 13 Q. Yes. Well, speaking of 14 methodology, though, Dr. Tuttle, we've gone 15 now to the source document, the IARC 16 Monograph 93, and we've found at 411 the 17 source sentence for your quotation, fair? 18 A. Yes. 19 Q. And you told me, in looking 20 together at 411, you did not see any studies 21 cited, correct? 22 A. Yes, that's correct. 23 Q. But if we go back to 392, we do 24 find studies, beginning with the Egli and</p>	<p>1 references cited by them. I don't claim to 2 have cited every reference that IARC cites in 3 their monograph in my report. 4 BY MR. SOILEAU: 5 Q. But you quoted IARC for the 6 conclusion, yet you didn't independently 7 review the studies upon which their 8 conclusion was based, did you? 9 MR. FROST: Objection. 10 A. Well, again, you're stating 11 that, you handed me just a small handful of 12 studies. We can go through all the 13 references that they cite and then look also 14 at my report and see which references they 15 cite and which ones I cite and which ones 16 they do and I do not. 17 As I said before, you know, you 18 look at the data and you look at the 19 scientific evidence, and the example you keep 20 using of Egli and Newton, as I said before, 21 one, is looking at inert carbon particles; 22 two, looking at deposition in the vagina as 23 opposed to external perineal application; 24 three, as it says in two of three patients</p>

Kelly Tuttle, Ph.D.

Page 190	Page 192
<p>1 traveled to the fallopian tubes. It doesn't</p> <p>2 mention the ovaries specifically here.</p> <p>3 BY MR. SOILEAU:</p> <p>4 Q. Do you see the reference later</p> <p>5 in that same paragraph of page 392 of the</p> <p>6 IARC Monograph 93 to Henderson, et al, 1971?</p> <p>7 A. Yes, I do.</p> <p>8 Q. And I've presented you with a</p> <p>9 Henderson 1971 paper. It's now marked as</p> <p>10 Tuttle Exhibit 14, right?</p> <p>11 A. I don't recall the exhibit</p> <p>12 number, but yes, you presented Henderson 1971</p> <p>13 to me.</p> <p>14 Q. Right. And you confirmed that</p> <p>15 you did not look at that paper either, right?</p> <p>16 MR. FROST: Objection.</p> <p>17 A. Again, I did not cite it in my</p> <p>18 report.</p> <p>19 BY MR. SOILEAU:</p> <p>20 Q. And if it's not cited, you</p> <p>21 didn't look at it. I mean, if you looked at</p> <p>22 it, you would have cited it, right?</p> <p>23 A. Well, as I said, I would need</p> <p>24 to refamiliarize -- or I would need to go</p>	<p>1 articles, so it would be -- I can't say</p> <p>2 specifically that I looked at it, read it and</p> <p>3 placed it to the side.</p> <p>4 But that being said, I could</p> <p>5 very easily have looked at it and said this</p> <p>6 is not addressing external perineal</p> <p>7 application of talcum powder and migration to</p> <p>8 the ovaries; therefore, it's no evidence that</p> <p>9 supports the migration theory, and therefore</p> <p>10 didn't cite it in my report.</p> <p>11 Q. And then you would kick it out</p> <p>12 of the materials considered?</p> <p>13 A. Again, in the references, those</p> <p>14 are the references that I cite in my report,</p> <p>15 those are the references that I put into the</p> <p>16 report.</p> <p>17 Q. That are helpful?</p> <p>18 MR. FROST: Objection.</p> <p>19 A. No, they're the references that</p> <p>20 I cite in the report.</p> <p>21 BY MR. SOILEAU:</p> <p>22 Q. Well, I understand there are</p> <p>23 thousands of papers out there. I'm just</p> <p>24 trying to understand what we have, because I</p>
Page 191	Page 193
<p>1 back and look at these articles that you are</p> <p>2 placing in front of me because I don't cite</p> <p>3 them in my report, which means -- meaning</p> <p>4 that I don't reference them.</p> <p>5 That being said, you know, I</p> <p>6 need to look at them and look at what the</p> <p>7 basis for them is and understand, and then I</p> <p>8 can have a better ability to discuss why they</p> <p>9 weren't cited or why they weren't referenced</p> <p>10 in my report.</p> <p>11 Q. Is it possible that you pulled</p> <p>12 the Henderson 1971 paper, looked at it,</p> <p>13 considered it, then set it aside and did not</p> <p>14 include it in your references of materials</p> <p>15 considered?</p> <p>16 MR. FROST: Objection.</p> <p>17 BY MR. SOILEAU:</p> <p>18 Q. I just need to know if I can</p> <p>19 rely on the references as a complete listing</p> <p>20 of the scientific literature, the scientific</p> <p>21 evidence that was gathered and considered.</p> <p>22 A. Well, as I've said before, in</p> <p>23 going through the scientific evidence, you're</p> <p>24 dealing with thousands upon millions of</p>	<p>1 may have misunderstood what your reference</p> <p>2 list is.</p> <p>3 I would have assumed that if</p> <p>4 you did a search of the thousands of papers</p> <p>5 and you found Henderson 1971, and for the</p> <p>6 reasons you've told us, you didn't think it</p> <p>7 proved migration or even supported migration,</p> <p>8 you would nonetheless include it among the</p> <p>9 reference materials as something that you had</p> <p>10 identified and considered. Am I wrong?</p> <p>11 MR. FROST: Objection.</p> <p>12 A. Again, without giving me an</p> <p>13 opportunity to read Henderson, I can't speak</p> <p>14 to it specifically. What I'm saying is that</p> <p>15 in doing an assessment of science, I'd need</p> <p>16 to know, you know, what Henderson is actually</p> <p>17 looking at, what their tests are, what -- you</p> <p>18 know, and have an opportunity to actually</p> <p>19 review the article.</p> <p>20 BY MR. SOILEAU:</p> <p>21 Q. Right. But I might have</p> <p>22 thought you did that before you formed your</p> <p>23 opinion.</p> <p>24 MR. FROST: Objection.</p>

49 (Pages 190 to 193)

Kelly Tuttle, Ph.D.

<p>Page 194</p> <p>1 BY MR. SOILEAU: 2 Q. Well, see, here's my problem. 3 Based on your testimony this afternoon, I'm 4 no longer comfortable that I know whether you 5 looked at Henderson or not because it seems 6 you're telling me you may have found the 7 Henderson '71 paper, which is now Tuttle 8 Exhibit 14, looked at it, concluded it did 9 not support a relationship between perineal 10 application and migration, and therefore set 11 it aside so that it didn't make it into the 12 reference list. Is that possible? 13 MR. FROST: Objection, 14 misstates testimony. 15 BY MR. SOILEAU: 16 Q. I don't mean to state your 17 testimony or rephrase your testimony. It's a 18 question: Is it possible that in reviewing 19 available literature, Henderson '71 was 20 found, the same Henderson '71 that is now 21 Tuttle Exhibit 14, that it was found, that 22 you looked at it, and then you cast it away 23 and therefore did not put it on the reference 24 list. Is that possible?</p>	<p>Page 196</p> <p>1 tract to the ovaries. 2 Q. If I understand your testimony, 3 you're telling me that if you had come across 4 Henderson, you would not have considered it 5 relevant to the migration issue and therefore 6 it would not have been listed; is that fair? 7 A. Again, you'd need to let me 8 actually read Henderson and look at it to be 9 able to say I don't cite it in my report, so 10 I'm not familiar with the, you know, 11 objectives or methods that were used in the 12 study. 13 Q. Very well. 14 As we sit here today, last 15 question on this. I want to move on. Last 16 question on this, Doctor. 17 Do you know whether you ever 18 saw Henderson or not in the context of this 19 project, Henderson '71, Tuttle Exhibit 14, do 20 you know whether you ever looked at it before 21 or not? 22 MR. FROST: Objection. 23 A. I don't recall. 24 ///</p>
<p>Page 195</p> <p>1 MR. FROST: Objection. 2 A. So I'll try to be very clear. 3 BY MR. SOILEAU: 4 Q. Good. That will help. 5 A. What I'm trying to explain is 6 that in looking at the migration theory and 7 the theory that external application of talc 8 can migrate to the ovaries and looking at the 9 scientific literature, and in my references 10 or looking at IARC, I attempted to look at 11 the scientific literature that actually 12 examined the external application of talc and 13 the potential for migration to the ovaries. 14 So if the -- if there's studies 15 that look at other -- other things as we've 16 talked about, vaginal insertion or, you 17 know -- and again, I would need to look at 18 these articles specifically to be able to 19 speak to Henderson, which is the one we're 20 discussing right now. 21 But generally speaking, there 22 is no scientific evidence that has examined 23 that external perineal application and 24 migration through the female reproductive</p>	<p>Page 197</p> <p>1 BY MR. SOILEAU: 2 Q. Okay. Let me show you 3 something that's been marked as Tuttle 4 Exhibit 20. 5 (Whereupon, Deposition Exhibit 6 Tuttle-20, Ovarian Cancer Prevention 7 (PDR) Patient Information, was marked 8 for identification.) 9 BY MR. SOILEAU: 10 Q. Do you know if you've seen this 11 item previously? 12 A. I think I have seen it before, 13 yes. 14 Q. Do you know who NCI is or what 15 NCI is? It's not a trick question. It's on 16 here. I should say: Do you recognize NCI as 17 the National Cancer Institute? The print is 18 very small, but if you look below the 19 heading -- let me show you where. It's on 20 there. 21 Do you see that? 22 A. Yes. 23 Q. Not to read, just to locate. 24 Go ahead and look at your copy. So let me</p>

Kelly Tuttle, Ph.D.

<p style="text-align: right;">Page 198</p> <p>1 get a fair question to you, because I don't</p> <p>2 think we have one on the table at this</p> <p>3 moment.</p> <p>4 Doctor, do you recognize the</p> <p>5 entity known as the National Cancer</p> <p>6 Institute?</p> <p>7 A. Yes, I'm familiar with the</p> <p>8 National Cancer Institute.</p> <p>9 Q. Do you recognize PDQ as</p> <p>10 something associated with the National Cancer</p> <p>11 Institute? You'll see that it appears here</p> <p>12 on the top title of this document, PDQ, and</p> <p>13 it has the R for restricted use.</p> <p>14 Do you know what that is?</p> <p>15 A. I don't think the R is</p> <p>16 restricted. I thought it was a registered.</p> <p>17 Q. Oh, registered. I'm sorry,</p> <p>18 you're right. It's later in the day. You're</p> <p>19 doing better than me. That's why you're</p> <p>20 answering questions and I'm asking them.</p> <p>21 Okay. Registered. So NCI has</p> <p>22 registered PDQ. Do you know what it means?</p> <p>23 A. Not specifically. This appears</p> <p>24 to be a website with some patient</p>	<p style="text-align: right;">Page 200</p> <p>1 behind the -- that talc section as you</p> <p>2 described it. I haven't had a chance to look</p> <p>3 at it in more detail. This isn't something</p> <p>4 that -- it's not a scientific article. I</p> <p>5 don't see any data included here.</p> <p>6 BY MR. SOILEAU:</p> <p>7 Q. Would you give any weight to</p> <p>8 this statement by the National Cancer</p> <p>9 Institute?</p> <p>10 MR. FROST: Objection.</p> <p>11 A. As I've said previously, with</p> <p>12 any agency with statements, I want to look at</p> <p>13 the science and the data that they are using</p> <p>14 or citing, and with this website, this isn't</p> <p>15 a study, and I don't see any citations or</p> <p>16 anything specifically that they put forward</p> <p>17 for that section other than those sentences.</p> <p>18 BY MR. SOILEAU:</p> <p>19 Q. Did you, in your report,</p> <p>20 actually cite governmental and agency</p> <p>21 summaries?</p> <p>22 A. I'd have to look specifically,</p> <p>23 but I -- as I've -- you know, we stated</p> <p>24 before, I cite IARC and I cite other</p>
<p style="text-align: right;">Page 199</p> <p>1 information.</p> <p>2 Q. Okay.</p> <p>3 A. I do not know what PDQ stands</p> <p>4 for.</p> <p>5 Q. Very well.</p> <p>6 Look at page 3 of this item</p> <p>7 under Talc, and see what the National Cancer</p> <p>8 Institute has said about talc.</p> <p>9 MR. FROST: Objection.</p> <p>10 BY MR. SOILEAU:</p> <p>11 Q. Talc. The use of talc may</p> <p>12 increase the risk of ovarian cancer. Talcum</p> <p>13 powder dusted on the perineum (the area</p> <p>14 between the vagina and the anus) may reach</p> <p>15 the ovaries by entering the vagina.</p> <p>16 That's the end of the quote.</p> <p>17 Have you considered this</p> <p>18 before, this language from the NCI website,</p> <p>19 as you examined scientific evidence and</p> <p>20 reached your opinions?</p> <p>21 MR. FROST: Objection to form.</p> <p>22 A. Well, as I mentioned, this</p> <p>23 appears to be a website for general patient</p> <p>24 information. I don't see any references</p>	<p style="text-align: right;">Page 201</p> <p>1 government agencies as well.</p> <p>2 Q. Look at the table of contents,</p> <p>3 II, and see what 7.3.3 is. I'm sorry, did</p> <p>4 you see?</p> <p>5 A. Yes.</p> <p>6 Q. It's a review of governmental</p> <p>7 and agency summaries, isn't it?</p> <p>8 A. Yes, that's what the title is.</p> <p>9 Q. Okay. Let me show you a new</p> <p>10 exhibit. I'm sorry, I've been annoyed at the</p> <p>11 little ding that I'm hearing, and I didn't</p> <p>12 know where it was coming from and now I know,</p> <p>13 it's coming from my pocket. I apologize to</p> <p>14 everyone. I was listening to some music at</p> <p>15 the break, so I turned the sound back on.</p> <p>16 (Whereupon, Deposition Exhibit</p> <p>17 Tuttle-21, Health Canada Draft</p> <p>18 Screening Assessment, was marked for</p> <p>19 identification.)</p> <p>20 BY MR. SOILEAU:</p> <p>21 Q. I've marked an exhibit as</p> <p>22 Tuttle Exhibit 21, and I'm going to ask you,</p> <p>23 Doctor, if you recognize this as the draft</p> <p>24 assessment from Health Canada?</p>

51 (Pages 198 to 201)

Kelly Tuttle, Ph.D.

Page 202	Page 204
<p>1 A. Yes.</p> <p>2 Q. Now, this is something that</p> <p>3 appears in your reference materials, isn't</p> <p>4 it?</p> <p>5 A. Yes, I believe it does.</p> <p>6 Q. And I think you told me that</p> <p>7 you added Taher, the Taher paper, to your</p> <p>8 supplemental materials after you saw some</p> <p>9 discussion of both Health Canada and Taher in</p> <p>10 some of the depositions, I assume; is that</p> <p>11 right?</p> <p>12 A. In some -- yes.</p> <p>13 Q. Somewhere?</p> <p>14 A. Either in depositions or the</p> <p>15 reports. I don't recall specifically.</p> <p>16 Q. Okay. But regardless, you've</p> <p>17 now looked at both Taher and Health Canada,</p> <p>18 and you had included Health Canada in the</p> <p>19 reference materials for your original report?</p> <p>20 A. That's correct.</p> <p>21 Q. Okay. Let's go to pages 19, 20</p> <p>22 and 21, and I'm really starting on the bottom</p> <p>23 of 19. You see the sentence that says: The</p> <p>24 most recent meta-analysis, Taher, et al.</p>	<p>1 Let's turn to page 21 now, if</p> <p>2 we could. And you see a paragraph near the</p> <p>3 top of page 21 that begins with the words</p> <p>4 Biological Plausibility?</p> <p>5 A. Yes.</p> <p>6 Q. And that's what we're talking</p> <p>7 about. I mean, that's -- we sort of launched</p> <p>8 into a long discussion before our most recent</p> <p>9 break, but we were talking about plausibility</p> <p>10 or, as you say in your report at page 5,</p> <p>11 biological plausibility under the Hill paper</p> <p>12 and viewpoints, fair?</p> <p>13 A. Yes.</p> <p>14 Q. Okay. So you have considered</p> <p>15 what Health Canada has said about biological</p> <p>16 plausibility and specifically migration,</p> <p>17 correct?</p> <p>18 MR. FROST: Objection.</p> <p>19 A. I would -- again, I would need</p> <p>20 to look at my report. If -- I certainly am</p> <p>21 familiar with the Health Canada document, but</p> <p>22 again, I don't know. I'm sorry, I don't know</p> <p>23 that I understand what you're referring to as</p> <p>24 far as how I used the Health Canada document.</p>
Page 203	Page 205
<p>1 2018?</p> <p>2 A. Yes, I see that.</p> <p>3 Q. That's the Taher paper that you</p> <p>4 added in your supplemental materials?</p> <p>5 A. I believe so, yes.</p> <p>6 Q. And it goes on to say, in part,</p> <p>7 employed the Hill criteria, Hill 1965, and of</p> <p>8 course, that's the Sir Arthur Bradford Hill</p> <p>9 paper that we've discussed?</p> <p>10 A. Again, without flipping to the</p> <p>11 references, I believe so.</p> <p>12 Q. Okay. Look at the next</p> <p>13 paragraph, 19. You see Strength as a topic?</p> <p>14 A. Yes.</p> <p>15 Q. And then on page 20 you see the</p> <p>16 topics of Consistency, Specificity,</p> <p>17 Temporality and Biological Gradient?</p> <p>18 A. Yes.</p> <p>19 Q. Do you recognize those topics</p> <p>20 from the Hill paper?</p> <p>21 A. Yes. Those are all some of</p> <p>22 the -- a portion of the nine viewpoints put</p> <p>23 forth by the Hill criteria.</p> <p>24 Q. Very well.</p>	<p>1 BY MR. SOILEAU:</p> <p>2 Q. That's fine. That's a fault</p> <p>3 with my questioning then, and let me fix it.</p> <p>4 If something is on the</p> <p>5 reference list that is attached to your</p> <p>6 report, Doctor, does it mean that you</p> <p>7 reviewed it, or is it possible that it's on</p> <p>8 the list but you never looked at it?</p> <p>9 MR. FROST: Objection.</p> <p>10 A. So everything that is cited in</p> <p>11 my report I have reviewed or read. Now,</p> <p>12 there's a large number of articles on there,</p> <p>13 so, you know, it may have been some time</p> <p>14 since they've been read or anything like</p> <p>15 that.</p> <p>16 BY MR. SOILEAU:</p> <p>17 Q. Okay. And I -- to be fair, I</p> <p>18 particularly didn't ask how much time or how</p> <p>19 in depth you read each one, but I did want to</p> <p>20 note that you did at least consider to some</p> <p>21 extent each of the items included in the</p> <p>22 reference materials; is that fair? You did?</p> <p>23 A. Yes, as I said, if they're</p> <p>24 cited in my report, I've referred to them, I</p>



Kelly Tuttle, Ph.D.

Page 206	Page 208
<p>1 have at least read them. As I said, it may</p> <p>2 have been some time previously. It may have</p> <p>3 been a brief review versus an in-depth, but I</p> <p>4 have read all the articles that I cite in my</p> <p>5 report.</p> <p>6 Q. Okay. Let's look at what</p> <p>7 Health Canada said on page 21 under</p> <p>8 Biological plausibility. Particles of talc</p> <p>9 are hypothesized to migrate into the pelvis</p> <p>10 and ovarian tissue, causing irritation and</p> <p>11 inflammation. The presence of talc in the</p> <p>12 ovaries has been documented (Heller,</p> <p>13 H-E-L-L-E-R, et al, 1996b). This evidence of</p> <p>14 retrograde transport supports the biological</p> <p>15 plausibility of the association between</p> <p>16 perineal talc application and ovarian</p> <p>17 exposure.</p> <p>18 Did I read that portion of the</p> <p>19 paragraph correctly?</p> <p>20 A. Yes, but you stopped</p> <p>21 mid-sentence there at the end.</p> <p>22 Q. Let me keep going then. We'll</p> <p>23 go all the way to the end of the paragraph.</p> <p>24 However, the specific</p>	<p>1 Did you give any weight to this</p> <p>2 statement by Health Canada?</p> <p>3 MR. FROST: Objection.</p> <p>4 A. Well, again, as I've stated</p> <p>5 before, in any of the government or</p> <p>6 regulatory agencies, when reviewing their</p> <p>7 documents and summaries, I try to look at the</p> <p>8 data that either supports or doesn't support</p> <p>9 their statements or the references they cite.</p> <p>10 In this particular paragraph,</p> <p>11 they cite the Heller study, which I believe I</p> <p>12 cite in my report.</p> <p>13 Q. You do.</p> <p>14 A. And as well as the Taher</p> <p>15 meta-analysis, and to be clear, the Heller</p> <p>16 study, I would need to have it in front of</p> <p>17 me, but it states here, only looks at the</p> <p>18 presence of talc in the ovaries. It does not</p> <p>19 document or assess external application and</p> <p>20 migration, and the Taher study, as I</p> <p>21 understand, is a meta-analysis of the</p> <p>22 epidemiological studies, so again, does not</p> <p>23 assess the migration theory.</p> <p>24 Q. Doctor, in your opinion, has</p>
Page 207	Page 209
<p>1 mechanism(s) and cascade of molecular events</p> <p>2 by which talc may cause ovarian cancer have</p> <p>3 not been identified (Taher et al, 2018).</p> <p>4 Now, we've read the entire</p> <p>5 section on biological plausibility, correct?</p> <p>6 A. Well, we've read that entire</p> <p>7 paragraph where it specifically addresses</p> <p>8 biological plausibility in that specific --</p> <p>9 Q. Fair. Right. I didn't mean to</p> <p>10 say that there's no mention of plausibility</p> <p>11 elsewhere in the paper. I just meant that</p> <p>12 we've gone through the Hill viewpoints. We</p> <p>13 got to biological plausibility, and I just</p> <p>14 read the section on biological plausibility.</p> <p>15 The next thing in Health Canada</p> <p>16 on page 21 is Coherence, another viewpoint,</p> <p>17 right?</p> <p>18 A. Yes. As I said, on that</p> <p>19 particular page. I don't recall if it's</p> <p>20 discussed in more detail elsewhere in the</p> <p>21 report, but in this particular section,</p> <p>22 you've read the entirety of the plausibility</p> <p>23 paragraph.</p> <p>24 Q. Thank you.</p>	<p>1 talc been found in ovarian tissue?</p> <p>2 A. Well, I --</p> <p>3 MR. FROST: Objection.</p> <p>4 THE WITNESS: Sorry.</p> <p>5 A. Again, as I stated, there have</p> <p>6 been studies that have looked at talc in</p> <p>7 ovarian tissue -- we'd have to look at those</p> <p>8 individual studies, you know, but -- has seen</p> <p>9 it, but again, has not been looking at the</p> <p>10 external perineal application and migration.</p> <p>11 BY MR. SOILEAU:</p> <p>12 Q. Yes, Doctor. This is a</p> <p>13 different question, though. I'm not asking</p> <p>14 you about the migration at this moment. I'm</p> <p>15 asking you specifically, based on your review</p> <p>16 of the scientific evidence and literature,</p> <p>17 has talc been found in the ovaries of women?</p> <p>18 MR. FROST: Objection.</p> <p>19 A. Again, I'd have to look at the</p> <p>20 scientific evidence from a different angle as</p> <p>21 you said because as I said before, I've been</p> <p>22 looking at the evidence for migration theory</p> <p>23 from external application.</p> <p>24 I certainly am aware, as you</p>



Kelly Tuttle, Ph.D.

<p style="text-align: right;">Page 210</p> <p>1 say, like in the Heller study and in other 2 studies, they have been looking for and 3 through their various methods have surmised 4 that they have identified talc in the 5 ovaries, but that was not my specific 6 objective. It was looking at the migration 7 theory rather than just the presence of talc 8 in the ovaries, because we kind of discussed 9 that earlier, that the presence of talc in 10 the ovaries is not sufficient to indicate, or 11 of any chemical on an organ, to indicate that 12 an adverse health effect will occur. 13 BY MR. SOILEAU: 14 Q. Do you believe that talc has 15 been found in the ovaries of women who have 16 had their ovarian tissue examined based on 17 your review of the scientific evidence? 18 MR. FROST: Objection. 19 BY MR. SOILEAU: 20 Q. I'm not asking about migration. 21 I'm not asking about carcinogenicity right 22 now. I'm asking you, based on your review of 23 the scientific evidence, has talc, talc 24 particles as you say in your report, been</p>	<p style="text-align: right;">Page 212</p> <p>1 BY MR. SOILEAU: 2 Q. That is the Heller paper cited 3 at page 21? 4 A. Yes, I cited it in my report. 5 Q. If I asked you to assume that 6 talc particles have been identified in 7 ovarian tissue, what explanation would you 8 offer to help us understand how it got there? 9 MR. FROST: Objection, outside 10 of the scope of this witness' opinions 11 being offered in this case. 12 BY MR. SOILEAU: 13 Q. Well, do you think that's 14 outside the scope of your expertise or 15 opinions, talking about how it gets there? 16 A. Well, as I said, I was asked to 17 look at the potential causal association 18 between perineal talcum powder exposure and 19 ovarian cancer. A small subset of that in 20 Hill criteria is biological plausibility. 21 So I assessed the scientific 22 evidence on whether the mechanism of external 23 application and migration to the ovaries has 24 been -- if there's been any evidence in the</p>
<p style="text-align: right;">Page 211</p> <p>1 found in -- embedded in ovarian tissue? 2 MR. FROST: Objection. 3 A. Well, again, in this particular 4 report and in this -- because I did not do an 5 assessment regarding just the presence of 6 talc in the ovarian tissue. We can refer to 7 my report where I discuss it in more detail 8 regarding those things. 9 I think others involved in this 10 litigation get more in detail into that. I 11 merely looked at it through the lens of the 12 Hill criteria as far as the migration theory 13 that perineal application can migrate to the 14 ovaries. 15 Q. You say this particular report. 16 You're talking about the report that you 17 authored and signed in this litigation? 18 A. Yes, I'm referring to -- to the 19 objectives of my scientific -- the research 20 that I put in my report. 21 Q. You did look at Heller, didn't 22 you? 23 MR. FROST: Objection. 24 ///</p>	<p style="text-align: right;">Page 213</p> <p>1 scientific literature to support that 2 external migration, which I state my opinion 3 has not. 4 But regarding just the -- you 5 know, alternative -- as you said, the 6 presence of talc in the ovaries and how it 7 gets there is -- I don't believe I -- beyond 8 the realm of talcum powder and external 9 migration, I'm not sure that I assess any of 10 that in my report, and I didn't look at 11 alternative talc exposures or other potential 12 sources of talc or things of that nature. 13 Q. Let me understand, Doctor. You 14 looked to see if talcum powder applied to the 15 perineum could migrate through the vaginal 16 tract to the ovaries, fair? 17 A. So what I looked at is we -- 18 you have the hypothesis -- 19 Q. Yes. 20 A. -- that talcum powder applied 21 to the perineum can enter the vagina and pass 22 through the female reproductive tract to the 23 ovaries. 24 What I have done under the</p>

54 (Pages 210 to 213)

Kelly Tuttle, Ph.D.

<p>Page 214</p> <p>1 biological plausibility is look to see if 2 there's any data to support that hypothesis 3 that the external application of talcum 4 powder can enter the vagina and migrate to 5 the ovaries. 6 Q. Well, wouldn't evidence of talc 7 in the ovaries be relevant to the discussion 8 and investigation of whether talcum powder 9 can migrate through the vagina to the 10 ovaries? 11 MR. FROST: Objection. 12 A. Well, it would depend. You 13 know, as we talked about with some of the 14 studies that you placed in front of me 15 earlier, we're talking about, you know, 16 vaginal insertion or, you know, other 17 scenarios that are different from just 18 perineal application. 19 So it would depend on the 20 nature of the study and the nature of the 21 assessment to determine whether it would be 22 applicable. 23 BY MR. SOILEAU: 24 Q. But you haven't looked.</p>	<p>Page 216</p> <p>1 their -- what they did. I know they went 2 more -- as I said, I believe there are others 3 who have gone into more detail, and so I 4 would refer to their work. Because as I 5 said, I just looked at the scientific 6 evidence for an external application 7 migration hypothesis. 8 Q. We talked about Johnson &amp; 9 Johnson documents. Were you provided with 10 any Imerys documents? 11 A. I believe there are some Imerys 12 documents put in my -- on my materials relied 13 and reviewed upon. Anything I was provided 14 is listed there on my report. 15 Q. Okay. Those are the materials 16 regarding the analysis of the content of the 17 talcum powder products and the makeup of 18 fragrances? 19 A. Yes, that's correct. I believe 20 so. 21 Q. And by that, I simply mean the 22 appendices on those issues, and those, you're 23 telling me, might include some reference to 24 Imerys documents in part.</p>
<p>Page 215</p> <p>1 MR. FROST: Objection. 2 BY MR. SOILEAU: 3 Q. You haven't looked at the 4 scientific literature and evidence to form an 5 opinion on whether talc is found in the 6 ovaries of women; is that correct? 7 MR. FROST: Objection. 8 A. Again, I looked at the 9 scientific evidence to see whether there have 10 been any scientific evidence to support that 11 talcum powder applied externally to the 12 perineum can enter the vagina and transport 13 through the female reproductive tract to the 14 ovaries. 15 I think that there are others 16 involved in this litigation that get more 17 into some of the questions you're asking, and 18 so I would probably -- have to refer to their 19 work and then again look at what they cite to 20 do that type of assessment. 21 BY MR. SOILEAU: 22 Q. You would have to rely on what 23 they say? 24 A. No, I said I would refer to</p>	<p>Page 217</p> <p>1 Do I have it right? 2 A. I'm sorry. 3 Q. You want me to try again? 4 A. Please. 5 Q. It's possible that you have 6 some Imerys documents referenced in some of 7 the appendices to your report, fair? 8 A. Yes, and... 9 Q. Let me show you a document that 10 I've marked as Tuttle Exhibit 22. It's Bates 11 numbered as JNJ_000704 through 709 12 consecutively, and ask if you've seen this 13 document before. 14 (Whereupon, Deposition Exhibit 15 Tuttle-22, 2004 Fax Transmission of 16 Sj?sten Publication, was marked for 17 identification.) 18 A. No, I'm not familiar with this 19 document. 20 BY MR. SOILEAU: 21 Q. Okay. Let's look at on the 22 first page, you see what I've highlighted on 23 the screen just to give us a sense of where 24 I'm at? I'm reading here. I tell you what.</p>

Kelly Tuttle, Ph.D.

Page 218	Page 220
<p>1 I'll read the entire note.</p> <p>2 I came across this paper this</p> <p>3 morning published in the April 2004 journal,</p> <p>4 Human Reproduction, an official journal of</p> <p>5 the European Society for Human Reproduction</p> <p>6 and Embryology. It offers some compelling</p> <p>7 evidence in support of the, quote, migration,</p> <p>8 closed quote, hypothesis. Combine this, open</p> <p>9 quotes, evidence, closed quotes, with the</p> <p>10 theory that talc deposition on the ovarian</p> <p>11 epithelium initiates epithelium</p> <p>12 inflammation - which leads to epithelium</p> <p>13 carcinogenesis - and you have a potential</p> <p>14 formula for NTP classifying talc as a</p> <p>15 causative agent in ovarian cancer.</p> <p>16 Did I read that correctly,</p> <p>17 Doctor?</p> <p>18 A. Yes, you read that correctly,</p> <p>19 but this appears to be a personal</p> <p>20 communication with some personal conclusions</p> <p>21 and opinions. I don't know, you know, the</p> <p>22 basis for all of those statements or</p> <p>23 conclusions. As you say, he attaches the --</p> <p>24 and I'm not going to be able to pronounce the</p>	<p>1 A. I've not seen the public -- the</p> <p>2 publication date on the papers attached right</p> <p>3 here on the top.</p> <p>4 Q. Right. But I gave you the</p> <p>5 paper as Tuttle Exhibit 18, if it helps. It</p> <p>6 will be much easier to read, I think, than</p> <p>7 the small print on what is now Tuttle</p> <p>8 Exhibit 22.</p> <p>9 This is a pretty important</p> <p>10 statement if it's accurate, isn't it?</p> <p>11 MR. FROST: Objection.</p> <p>12 BY MR. SOILEAU:</p> <p>13 Q. Well, if -- I mean, doesn't</p> <p>14 this statement on Tuttle Exhibit 22 cause you</p> <p>15 to want to pause and revisit the question of</p> <p>16 migration?</p> <p>17 MR. FROST: Objection.</p> <p>18 A. Again, as I said earlier, this</p> <p>19 is a personal communiqué?. There are several</p> <p>20 statements and "mays" and, you know,</p> <p>21 "potential" and, you know, things, and this</p> <p>22 is just one article that they cite. I don't</p> <p>23 know the context of this conversation. I</p> <p>24 don't know Mr. Zazenski, I don't know what</p>
Page 219	Page 221
<p>1 last name, but the S-J- --</p> <p>2 Q. Sj?sten?</p> <p>3 A. Yes, that we discussed earlier.</p> <p>4 Q. Right. So this is the paper we</p> <p>5 discussed earlier, which is now Tuttle</p> <p>6 Exhibit 18, that is, the Tuttle Exhibit 18 is</p> <p>7 apparently attached to this note from Richard</p> <p>8 J. Zazenski, Z-A-Z-E-N-S-K-I, director of</p> <p>9 product safety, to Bill Ashton, fair?</p> <p>10 MR. FROST: Objection.</p> <p>11 A. That's -- it appears that, yes,</p> <p>12 the article is attached to this</p> <p>13 communication.</p> <p>14 BY MR. SOILEAU:</p> <p>15 Q. And this Sj?sten paper is from</p> <p>16 2004?</p> <p>17 A. Again, this was not something I</p> <p>18 cited in my report, so I'm not --</p> <p>19 Q. I understand that. Go ahead.</p> <p>20 I'm sorry.</p> <p>21 A. -- very familiar with it. In</p> <p>22 the communiqué? it says published in</p> <p>23 April 2004. I --</p> <p>24 Q. Right. And you have the paper.</p>	<p>1 he's basing these statements on.</p> <p>2 And again, it's a personal</p> <p>3 communication. It's not a scientific article</p> <p>4 or a scientific journal beyond the one</p> <p>5 article that they -- he attaches in this</p> <p>6 communication.</p> <p>7 BY MR. SOILEAU:</p> <p>8 Q. Right. I understand what</p> <p>9 you're saying, Doctor, but doesn't this</p> <p>10 document at least cause you to wonder, to</p> <p>11 want to pause and do more investigation, to</p> <p>12 find out who Mr. Zazenski is, for example?</p> <p>13 MR. FROST: Objection.</p> <p>14 A. Again, it's an internal</p> <p>15 communication. It's not a scientific</p> <p>16 document. You know, it's not something that</p> <p>17 I would refer to in doing a review of the</p> <p>18 scientific literature.</p> <p>19 BY MR. SOILEAU:</p> <p>20 Q. If he was available, would you</p> <p>21 not want to ask him why he finds this paper</p> <p>22 to be compelling evidence in support of</p> <p>23 migration, the migration hypothesis?</p> <p>24 MR. FROST: Objection.</p>

Kelly Tuttle, Ph.D.

<p>Page 222</p> <p>1 A. Again, he makes several 2 statements, and -- without knowing the 3 references or the basis for his opinions, but 4 again, it's a -- his opinions. It's a 5 personal communication. It's not something I 6 would use in doing a scientific assessment. 7 BY MR. SOILEAU: 8 Q. Do you know who NTP is? It's 9 referenced at the second-to-last line of this 10 note to Mr. Ashton. 11 A. I know from my experience who 12 NTP would be, but I don't know if it's the 13 same organization, you know, as the -- 14 Mr. Zazenski is referring to. 15 Q. Who do you know it to be? 16 A. I know NTP to be the National 17 Toxicology Program. 18 Q. It would make sense, wouldn't 19 it, that that is who he is referring to? You 20 have a potential formula for NTP classifying 21 talc as a causative agent in ovarian cancer. 22 MR. FROST: Objection. 23 A. Again, I know who -- that's who 24 I would think NTP meant, but I'm not aware.</p>	<p>Page 224</p> <p>1 impossible, whatever remains, however 2 improbable, must be the truth." 3 A. I'm sorry, is there a question? 4 Q. Do you think that's good 5 guidance? 6 MR. FROST: Objection. 7 A. Well, again, you're taking the 8 summary statement of what he discusses in 9 plausibility where, you know, he says that it 10 depends on the biological knowledge of the 11 day, and he quotes several things, and that 12 is his summary statement regarding, you know, 13 looking at plausibility. 14 BY MR. SOILEAU: 15 Q. All right. Let's look at one 16 more. I'll mark this as Tuttle Exhibit 23. 17 (Whereupon, Deposition Exhibit 18 Tuttle-23, 4/1/14 FDA Letter, was 19 marked for identification.) 20 THE WITNESS: And if we may 21 after this one, can we take a short 22 break? 23 MR. SOILEAU: Absolutely. I 24 thought it was about time myself.</p>
<p>Page 223</p> <p>1 There may be other organizations that have 2 that same acronym. I don't know. 3 BY MR. SOILEAU: 4 Q. Let me show you another 5 statement in the Hill paper. He quotes 6 Holmes and Watson and says, quote, "When you 7 have eliminated the impossible, whatever 8 remains, however improbable, must be the 9 truth." 10 Do you see that? 11 A. I'm sorry, can you refer me to 12 the -- 13 Q. The exhibit number? 14 A. Yes, please. 15 Q. I'll be glad to. It is Tuttle 16 Exhibit 7. 17 A. Thank you. 18 Q. The paragraph says, in full, at 19 the top of page 10 on the right column: In 20 short, the association we observe may be one 21 new to science or medicine, and we must not 22 dismiss it too lightheartedly as just too 23 odd. As Sherlock Holmes advised Dr. Watson, 24 quote, "When you have eliminated the</p>	<p>Page 225</p> <p>1 BY MR. SOILEAU: 2 Q. Here is Exhibit 23. It is a 3 letter from the Food and Drug Administration. 4 I have a date of April 1, 2014. It's from 5 the Department of Health and Human Services. 6 Certainly you recognize the Food and Drug 7 Administration, correct? 8 A. Yes. 9 Q. Just as an entity? 10 A. Yes, I'm familiar with the 11 Food and Drug Administration or FDA. 12 Q. Okay. And do you recognize 13 that the Food and Drug Administration has 14 some jurisdiction or authority in connection 15 with cosmetic products? 16 MR. FROST: Objection. 17 BY MR. SOILEAU: 18 Q. If you know. You may not know. 19 A. I -- you know, I know that the 20 FDA has done several things in regards to 21 cosmetic products regarding a specific -- 22 specific authority or regulations. I 23 don't -- we'd have to be more specific. 24 That's a very kind of general, overarching...</p>

Kelly Tuttle, Ph.D.

<p style="text-align: right;">Page 226</p> <p>1 Q. Okay. Do you know whether 2 Shower to Shower and Johnson's baby powder 3 fall under the authority of the Food and Drug 4 Administration? 5 MR. FROST: Objection. 6 A. Specifically, I don't know. I 7 didn't look at that. 8 BY MR. SOILEAU: 9 Q. Okay. Let's look at page 5 of 10 7. And I'm going to direct you to this 11 paragraph, which is the third full paragraph. 12 It begins with: While there exists no direct 13 proof of talc in ovarian carcinogenesis. 14 By the way, we looked at 15 something earlier. Isn't it true that in 16 cancer, the mechanism, the exact mechanism is 17 often not known -- 18 MR. FROST: Objection. 19 BY MR. SOILEAU: 20 Q. -- but the association, the 21 relationship, the causal relationship can be 22 established? 23 A. Well, that's a very broad 24 statement. Previously when we were talking</p>	<p style="text-align: right;">Page 228</p> <p>1 lung cancer. 2 Q. Never mind. 3 It says, going on in this 4 paragraph: The potential for particles to 5 migrate from the perineum and vagina to the 6 peritoneal cavity is indisputable. It is 7 therefore plausible that perineal talc (and 8 other particulate) that reaches the 9 endometrial cavity, fallopian tubes, ovaries 10 and peritoneum, may elicit a foreign body 11 type reaction and inflammatory response that 12 in some exposed women may progress to 13 epithelial cancers. 14 Do you see that? 15 A. Yes, but you ended before the 16 last sentence of that paragraph. 17 Q. Sure. It goes on to say: 18 However, there has been no conclusive 19 evidence to support causality. 20 All right, now we've read the 21 entire paragraph and a couple of stops and 22 the document will speak for itself. 23 But it does say the potential 24 for particulates to migrate from the perineum</p>
<p style="text-align: right;">Page 227</p> <p>1 about the Hill criteria, as I said before, 2 you don't take any one particular criteria in 3 a vacuum. You look at all nine viewpoints, 4 the context and the body as itself. 5 And in areas where the strength 6 and consistency in association are very 7 strong, the evidence regarding a mechanism 8 may be not as strong -- 9 Q. Exactly. 10 A. -- and you have a very strong 11 evidence forward. If you don't have a strong 12 association or strong consistency or, you 13 know, strong strength of the association, 14 then the burden on the other criteria becomes 15 much greater as far as looking at the nine 16 criteria as a whole. 17 Q. So, for example, in smoking we 18 may not know the exact mechanism of the 19 carcinogenicity, but given the strength of 20 the association, there is no doubt that there 21 is a proper conclusion that smoking causes 22 lung cancer, as an example, fair? 23 A. I haven't researched the 24 mechanisms regarding cigarette smoking and</p>	<p style="text-align: right;">Page 229</p> <p>1 to the peritoneal cavity is indisputable, 2 doesn't it? 3 MR. FROST: Objection. 4 A. Again, that's what it states 5 here, but it doesn't provide any basis for 6 that statement. 7 BY MR. SOILEAU: 8 Q. And certainly you disagree with 9 that? 10 A. As I said, it's not for me to 11 agree or disagree. There's no basis for the 12 statement as put forward here for me to look 13 at the data that they used for this 14 particular statement, and as I've said 15 before, the scientific evidence does not 16 support the external application migration 17 theory for talcum powder. 18 Q. Well, Doctor, you've been put 19 forward as an expert witness in this case, 20 and you have told me that migration is 21 something that you have examined and will 22 comment on, and I'm simply asking: Is the 23 position that you have adopted in this 24 litigation on behalf of J&amp;J in conflict with</p>



Kelly Tuttle, Ph.D.

<p style="text-align: right;">Page 230</p> <p>1 what the FDA says here?</p> <p>2 MR. FROST: Objection.</p> <p>3 A. Well, as I said, this is one</p> <p>4 paragraph taken out of the entire document,</p> <p>5 and so without looking at the context and</p> <p>6 there's no references cited for me to look at</p> <p>7 their basis for this statement.</p> <p>8 As I've said before, the</p> <p>9 scientific evidence does not support the</p> <p>10 migration theory that external application of</p> <p>11 talc can migrate to the ovaries.</p> <p>12 BY MR. SOILEAU:</p> <p>13 Q. Can you say whether this</p> <p>14 paragraph conflicts with the opinions you</p> <p>15 have offered in this case and that we are</p> <p>16 discussing today?</p> <p>17 MR. FROST: Objection.</p> <p>18 A. Again, without looking at</p> <p>19 the -- you know, the document in its</p> <p>20 entirety, we're taking it out of context, I</p> <p>21 certainly agree with the statement there's</p> <p>22 been no evidence to support causality at the</p> <p>23 end of the paragraph and that there's no</p> <p>24 direct proof of talc and ovarian</p>	<p style="text-align: right;">Page 232</p> <p>1 excuse me, the scientific evidence does not</p> <p>2 support the external application of --</p> <p>3 migration theory that the external</p> <p>4 application can migrate through the female</p> <p>5 reproductive tract and reach the ovaries.</p> <p>6 But as I have -- I think I've</p> <p>7 also said before that the scientific evidence</p> <p>8 does not support a causal association between</p> <p>9 perineal talcum powder exposure and ovarian</p> <p>10 carcinogenesis.</p> <p>11 Q. Whether you agree or not, in</p> <p>12 this paragraph, the FDA is telling us that it</p> <p>13 is biologically plausible, that is, migration</p> <p>14 of talcum powder through the vagina to the</p> <p>15 ovaries is biologically plausible. FDA is</p> <p>16 telling us that here, whether you agree or</p> <p>17 not, isn't it?</p> <p>18 MR. FROST: Objection.</p> <p>19 A. Again, we've quoted the</p> <p>20 paragraph out of this letter --</p> <p>21 BY MR. SOILEAU:</p> <p>22 Q. Right.</p> <p>23 A. -- again, addressing petitions.</p> <p>24 There's -- again, we haven't looked at the</p>
<p style="text-align: right;">Page 231</p> <p>1 carcinogenesis.</p> <p>2 BY MR. SOILEAU:</p> <p>3 Q. So you agree -- I'm sorry.</p> <p>4 A. These -- well, these -- again,</p> <p>5 the scientific basis for this is not put in</p> <p>6 here. There's no references. We would need</p> <p>7 to look at all the data beyond -- you know,</p> <p>8 this is just a letter regarding, if I</p> <p>9 remember correctly, a petition, where they're</p> <p>10 addressing a petition, rather than a document</p> <p>11 that is doing any -- any testing.</p> <p>12 I think they summarize some</p> <p>13 information in here, but I'm not seeing, you</p> <p>14 know, references or -- you know, a set of</p> <p>15 scientific data to refer to or review as far</p> <p>16 as the scientific evidence.</p> <p>17 Q. But you're telling me at the</p> <p>18 same time, you certainly agree with the</p> <p>19 statement that there's been no evidence to</p> <p>20 support causality?</p> <p>21 A. Well, as I --</p> <p>22 Q. Is that right?</p> <p>23 A. As I said before, I have not</p> <p>24 found any scientific evidence that -- or,</p>	<p style="text-align: right;">Page 233</p> <p>1 scientific data behind the statements or</p> <p>2 behind any -- any of the other things that</p> <p>3 we've discussed.</p> <p>4 Q. Shouldn't you have done that</p> <p>5 before today?</p> <p>6 MR. FROST: Objection.</p> <p>7 A. Well, as I said previously,</p> <p>8 I've assessed the body of science in my</p> <p>9 report and looked at the external application</p> <p>10 of perineal talc and the potential migration</p> <p>11 to the ovaries as well as the other nine</p> <p>12 viewpoints of the Hill criteria and the --</p> <p>13 whether the scientific evidence is supportive</p> <p>14 of a causal association between perineal</p> <p>15 talcum powder exposure and ovarian cancer,</p> <p>16 for which the scientific evidence doesn't</p> <p>17 support that causal association.</p> <p>18 And the scientific evidence</p> <p>19 does not support the hypothesis that the</p> <p>20 external application of talcum powder cannot</p> <p>21 migrate -- or that can migrate to the ovary</p> <p>22 after external application.</p> <p>23 BY MR. SOILEAU:</p> <p>24 Q. Had you seen this document</p>

Kelly Tuttle, Ph.D.

Page 234	Page 236
<p>1 before today?</p> <p>2 A. Yes, I believe so.</p> <p>3 Q. Can you at least tell me then,</p> <p>4 having reviewed this document previously and</p> <p>5 having it before you today, that the FDA,</p> <p>6 regardless of whether you agree or disagree,</p> <p>7 that the FDA is finding biological</p> <p>8 plausibility in the context of that topic</p> <p>9 that we've discussed today in this letter?</p> <p>10 They're saying it is therefore plausible?</p> <p>11 MR. FROST: Objection.</p> <p>12 A. Well, again, this is -- this is</p> <p>13 a letter. This is a response to a petition.</p> <p>14 I don't see that this is a research article</p> <p>15 or a -- you know --</p> <p>16 BY MR. SOILEAU:</p> <p>17 Q. Can you even say, though,</p> <p>18 Doctor, what the letter says? Yes, it's a</p> <p>19 letter. Yes, it's a letter though from the</p> <p>20 FDA. No, it doesn't cite literature. But</p> <p>21 I'm asking you: Does the letter say it is</p> <p>22 biologically plausible?</p> <p>23 MR. FROST: Objection.</p> <p>24 A. Again, you know, we have read</p>	<p>1 find that the data submitted presented</p> <p>2 conclusive evidence of a causal association.</p> <p>3 Q. What methodology is it, Doctor,</p> <p>4 that allows you to quote this letter for that</p> <p>5 position, yet ignore the statement of</p> <p>6 plausibility in the same letter by FDA?</p> <p>7 MR. FROST: Objection.</p> <p>8 A. So again, I was asked to opine</p> <p>9 on the overarching scientific data, the body</p> <p>10 of science, regarding the causal association</p> <p>11 between talcum powder and ovarian cancer and</p> <p>12 the scientific evidence of whether it</p> <p>13 supported the hypothesis that there's an</p> <p>14 association.</p> <p>15 In looking at the body of</p> <p>16 evidence and looking at the Hill criteria and</p> <p>17 looking at all the criteria, that was my</p> <p>18 objective of which biological plausibility,</p> <p>19 you know, I address, again, is one portion.</p> <p>20 BY MR. SOILEAU:</p> <p>21 Q. Right, but in doing that, you</p> <p>22 cited --</p> <p>23 MR. FROST: Let her finish her</p> <p>24 answer.</p>
Page 235	Page 237
<p>1 the paragraph, and in the paragraph it</p> <p>2 doesn't say biologically plausible.</p> <p>3 BY MR. SOILEAU:</p> <p>4 Q. Okay. I mean, look at page 28</p> <p>5 of your report. Aren't you citing in the</p> <p>6 paragraph that begins: In 2014, the FDA --</p> <p>7 aren't you citing this very letter that I've</p> <p>8 marked as Tuttle Exhibit 23?</p> <p>9 A. Yes, I am. It's in the</p> <p>10 subsection we were discussing earlier</p> <p>11 entitled Governmental and Agency Summaries.</p> <p>12 Q. Right. And you quoted from</p> <p>13 this letter.</p> <p>14 A. Yes, I do.</p> <p>15 Q. Even though the letter doesn't</p> <p>16 include any citation or authority.</p> <p>17 A. Well, again, as I've said</p> <p>18 before, with governmental agencies and</p> <p>19 documents, I refer to them, I look at their</p> <p>20 information, and then I think it's important</p> <p>21 to look at the scientific data.</p> <p>22 But again, this, again, also</p> <p>23 finds that data submitted presented</p> <p>24 conclusive evidence -- or excuse me, did not</p>	<p>1 MR. SOILEAU: Go ahead, if</p> <p>2 you're not finished.</p> <p>3 A. And as I said previously and we</p> <p>4 talked about previously with the Hill</p> <p>5 criteria, you can't take one criteria in a</p> <p>6 vacuum and just examine that solely for the</p> <p>7 establishment of causation. You need to look</p> <p>8 at the entire context.</p> <p>9 So in this particular scenario</p> <p>10 where I was looking at this letter, I do cite</p> <p>11 that their -- you know, their overarchal</p> <p>12 conclusion regarding causal association, but</p> <p>13 again, my research is in the scientific</p> <p>14 literature and the peer-reviewed literature</p> <p>15 as far as these provide context and</p> <p>16 information.</p> <p>17 BY MR. SOILEAU:</p> <p>18 Q. But what you have done is you</p> <p>19 have, in fact, taken one statement from the</p> <p>20 FDA letter -- you've taken a statement from</p> <p>21 that letter from the FDA, cited it in support</p> <p>22 of no evidence of a causal association, and</p> <p>23 ignored its statement about biological</p> <p>24 plausibility when you tell us later that</p>

60 (Pages 234 to 237)

Kelly Tuttle, Ph.D.

<p style="text-align: right;">Page 238</p> <p>1 there's no evidence of plausible theory.  2 Haven't you done the very  3 thing -- you need me to say it over? You  4 took one part of this FDA letter and put it  5 in your report and relied on it, didn't you?  6 MR. FROST: Objection.  7 A. Well, again, as I stated  8 before, when looking at governmental agency  9 summaries and documents, you know, while I  10 refer to them and I look at their  11 conclusions, I look at the scientific data  12 that is the basis for those conclusions.  13 And in this particular section  14 that you're referring to with the FDA quote  15 that I used, the government and --  16 governmental and agency summaries, if -- I'm  17 jumping ahead in my report a little bit, but  18 I was looking at the --  19 BY MR. SOILEAU:  20 Q. Right.  21 A. -- determinations regarding a  22 causal association. In this particular  23 section, I'm addressing causal association,  24 not biological plausibility, which I indicate</p>	<p style="text-align: right;">Page 240</p> <p>1 know, I refer to several in this particular  2 section, and I cite several in my report.  3 MR. SOILEAU: All right. Let's  4 take our next break now. Thank you.  5 THE VIDEOGRAPHER: Going off  6 the record at 1:56 p.m.  7 (Recess taken, 1:56 p.m. to  8 2:07 p.m.)  9 THE VIDEOGRAPHER: We're back  10 on the record at 2:07 p.m.  11 BY MR. SOILEAU:  12 Q. Okay. Doctor, are you ready to  13 proceed?  14 A. Yes, I am.  15 Q. Very well. Thank you.  16 Would you consider evidence of  17 talc in the ovaries of women to be important,  18 relevant evidence that you would want to  19 consider in your evaluation of the causality  20 question that you described earlier?  21 MR. FROST: Objection.  22 A. So I think we discussed that  23 earlier in that the presence of talc in the  24 ovaries is -- does not necessarily mean that</p>
<p style="text-align: right;">Page 239</p> <p>1 later in my report.  2 Q. Yes, Doctor.  3 A. Which I state that no  4 scientific evidence supports the migration  5 theory.  6 Q. I got that.  7 A. What is stated here is not  8 scientific evidence. It's a sentence in a  9 letter.  10 Q. Yes. But these are all apples  11 from the same tree, the tree of this letter,  12 and you have used one of the apples that you  13 selected on causation and ignored an apple on  14 plausibility as part of your methodology,  15 haven't you?  16 MR. FROST: Objection.  17 A. No. Again, as I said, I looked  18 at the body of science and the scientific  19 evidence. The citing of this particular  20 quote for the FDA article under the  21 governmental agencies, as I said, it's about  22 the science and the body of science.  23 It's not about, you know, each  24 individual governmental agency of which, you</p>	<p style="text-align: right;">Page 241</p> <p>1 an adverse health effect will occur. We have  2 to look at the body of science as a whole and  3 the scientific literature beyond -- beyond  4 that to see if there is a causal association.  5 BY MR. SOILEAU:  6 Q. I understand that the presence  7 of talc in the ovaries does not end the  8 causal association analysis, but I'm asking  9 you if it is one step, one part of the  10 evidence that you, as a toxicologist, would  11 want to know about and to consider in your  12 work on this project.  13 A. So again, as I stated before, I  14 wanted to assess the hypothesis on whether  15 external perineal application of talcum  16 powder can cause migration to the ovaries,  17 for which the scientific evidence does not  18 support that hypothesis.  19 Q. I've heard that from you, but  20 that's not the question I'm asking you. I  21 really need you to answer my question; and  22 that is: If there is evidence, okay -- if  23 there is evidence of talc in ovaries, do you  24 simply say, well, that does not necessarily</p>

Kelly Tuttle, Ph.D.

<p style="text-align: right;">Page 242</p> <p>1 mean that an adverse health effect will</p> <p>2 occur, so we don't need to look at it?</p> <p>3 MR. FROST: Objection.</p> <p>4 BY MR. SOILEAU:</p> <p>5 Q. Is that consistent with the</p> <p>6 methodology that you've used here?</p> <p>7 MR. FROST: Objection.</p> <p>8 A. No. So what I'm saying is that</p> <p>9 the question that we are asking or the</p> <p>10 question that I was asking in doing my</p> <p>11 literature -- assessing the body of science</p> <p>12 is whether the perineal application of talcum</p> <p>13 powder is causally associated with ovarian</p> <p>14 cancer.</p> <p>15 The subpart of that, as we've</p> <p>16 been discussing, is whether the migration</p> <p>17 theory that the external application of</p> <p>18 talcum powder can migrate from the external</p> <p>19 genitals to the ovaries.</p> <p>20 When you ask about just the</p> <p>21 presence of talc in the ovaries, that is --</p> <p>22 you know, we need to look at the mechanism,</p> <p>23 not just the mere presence. That's what I</p> <p>24 mean when I say the presence does not mean an</p>	<p style="text-align: right;">Page 244</p> <p>1 ovarian tissue with talc, that is, the</p> <p>2 presence of talc in ovarian tissue, another</p> <p>3 subpart that you would and should consider in</p> <p>4 your analysis of these issues?</p> <p>5 A. So again -- and I don't have my</p> <p>6 words in front of me, but as I was talking</p> <p>7 about the question we're looking at is the</p> <p>8 association between talcum powder use</p> <p>9 perineally and ovarian cancer and whether</p> <p>10 there is scientific evidence that supports a</p> <p>11 causal association.</p> <p>12 So the presence of talc in the</p> <p>13 ovaries or evidence noting talc in the</p> <p>14 ovaries, as I said, we have to look at --</p> <p>15 that's one part of -- but as we were talking</p> <p>16 about with biological plausibility, we have</p> <p>17 to look at the hypothesis that talc, when</p> <p>18 applied externally to the perineum, can</p> <p>19 migrate to the ovaries. And the scientific</p> <p>20 evidence does not support that hypothesis.</p> <p>21 In regards to just the presence</p> <p>22 or absence of talcum powder on the ovaries,</p> <p>23 that's just a very, very general, you know,</p> <p>24 looking at the scientific literature, is it</p>
<p style="text-align: right;">Page 243</p> <p>1 adverse health effect will occur.</p> <p>2 We have to look at the</p> <p>3 scientific literature. We've talked a little</p> <p>4 bit about the plausibility, but also the Hill</p> <p>5 criteria, the epidemiology, the evidence,</p> <p>6 because the -- as opposed to just the mere</p> <p>7 presence.</p> <p>8 BY MR. SOILEAU:</p> <p>9 Q. You said that one part is</p> <p>10 migration, the issue of migration. Did I get</p> <p>11 that right?</p> <p>12 MR. FROST: Objection.</p> <p>13 A. I --</p> <p>14 BY MR. SOILEAU:</p> <p>15 Q. You said -- I'm sorry, I'm</p> <p>16 going to use your words so that we have it</p> <p>17 more fairly and correctly.</p> <p>18 The subpart as we've been</p> <p>19 discussing is migration. That's not a full</p> <p>20 quote, but I'm using your words to structure</p> <p>21 my question, to be fair.</p> <p>22 The subpart that we've been</p> <p>23 discussing is migration, the migration</p> <p>24 theory. I'm simply asking is the presence of</p>	<p style="text-align: right;">Page 245</p> <p>1 there, isn't there type of scenario as</p> <p>2 opposed to the specific question we're</p> <p>3 looking at regarding talcum powder use</p> <p>4 perineally and ovarian cancer, which is what</p> <p>5 I assessed the scientific literature for.</p> <p>6 And as I've said previously,</p> <p>7 you know, there are other that get into the</p> <p>8 biological plausibility, the migration theory</p> <p>9 in more detail than I do. But in the context</p> <p>10 of my report and in the context of the body</p> <p>11 of science, we're specifically looking at</p> <p>12 that relationship between perineal</p> <p>13 application and ovarian cancer.</p> <p>14 Q. Doctor, was it purposeful that</p> <p>15 you changed my question from talc in the</p> <p>16 ovarian tissue to talc on the ovary?</p> <p>17 MR. FROST: Objection.</p> <p>18 A. I'm sorry. That was not</p> <p>19 intentional.</p> <p>20 BY MR. SOILEAU:</p> <p>21 Q. Okay. Do you recognize a</p> <p>22 distinction there between talc in the ovarian</p> <p>23 tissue versus talc on the ovary?</p> <p>24 A. Again, that was just a -- I --</p>

Kelly Tuttle, Ph.D.

<p style="text-align: right;">Page 246</p> <p>1 no, there was --</p> <p>2 Q. Okay.</p> <p>3 A. -- that was not intentional to</p> <p>4 change it in that manner.</p> <p>5 Q. Okay. Well, in my review of</p> <p>6 the literature I've seen that distinction</p> <p>7 made, and that's why I was wondering if you</p> <p>8 were moving to a different issue. I was</p> <p>9 confused. It was a long answer.</p> <p>10 Is evidence of talc in the</p> <p>11 ovarian tissue evidence that you would</p> <p>12 consider in your analysis of the causation</p> <p>13 question?</p> <p>14 MR. FROST: Objection.</p> <p>15 A. Again, I would need more</p> <p>16 information. As I was talking about, we --</p> <p>17 in the causation question we're assessing,</p> <p>18 we're looking at perineal application of</p> <p>19 talcum powder and ovarian cancer.</p> <p>20 So just saying if the talc is</p> <p>21 present or not, we would need more</p> <p>22 information as far as using that, the</p> <p>23 scientific evidence for that in assessing a</p> <p>24 causal relationship between talcum powder and</p>	<p style="text-align: right;">Page 248</p> <p>1 for you.</p> <p>2 Do I have it correct now?</p> <p>3 MR. FROST: Objection.</p> <p>4 A. Well, as I said, I need more</p> <p>5 information about the scientific evidence</p> <p>6 that you're purporting.</p> <p>7 BY MR. SOILEAU:</p> <p>8 Q. Right. You need more</p> <p>9 information in order for that evidence to get</p> <p>10 inside the fence, to get within the body of</p> <p>11 scientific evidence that you're considering,</p> <p>12 fair?</p> <p>13 MR. FROST: Objection.</p> <p>14 A. I'm saying that I would need</p> <p>15 more evidence about -- about the evidence.</p> <p>16 You've made the statement of evidence that</p> <p>17 talc present in the ovaries, but I would need</p> <p>18 to look at the studies, look at the questions</p> <p>19 that are being asked in the studies, you</p> <p>20 know, what the data they used, the dataset</p> <p>21 itself, because again, we're looking at a</p> <p>22 specific question regarding perineal</p> <p>23 application of talcum powder and ovarian</p> <p>24 cancer, not just the potential presence of</p>
<p style="text-align: right;">Page 247</p> <p>1 ovarian cancer.</p> <p>2 Q. So to be clear, if all I have</p> <p>3 is there is evidence of talc, talc particles</p> <p>4 in the ovarian tissue, that standing alone is</p> <p>5 not enough to move the ball for you?</p> <p>6 MR. FROST: Objection.</p> <p>7 A. Again, you have to have more</p> <p>8 information. You have to look at the</p> <p>9 context. You have to look at the studies</p> <p>10 that you're referencing for scientific</p> <p>11 evidence. You have to look at it in the</p> <p>12 context of the question and the scientific</p> <p>13 evidence as a whole.</p> <p>14 BY MR. SOILEAU:</p> <p>15 Q. Right. And what I want to</p> <p>16 understand is the boundaries around, the</p> <p>17 fence line around the scientific evidence as</p> <p>18 a whole and what it takes to get within those</p> <p>19 boundaries.</p> <p>20 And what I hear you telling me</p> <p>21 is evidence of talc particles in ovarian</p> <p>22 tissue, just that, none of the other things</p> <p>23 you mentioned, context, so forth, that's not</p> <p>24 enough to get within that body of evidence</p>	<p style="text-align: right;">Page 249</p> <p>1 talc particles on or in the ovaries.</p> <p>2 BY MR. SOILEAU:</p> <p>3 Q. Do you recognize the name</p> <p>4 A.P. Wehner?</p> <p>5 A. No, I do not.</p> <p>6 Q. You do not?</p> <p>7 A. Huh-uh.</p> <p>8 Q. Let me show you what I'll mark</p> <p>9 as Tuttle Exhibit 24.</p> <p>10 (Whereupon, Deposition Exhibit</p> <p>11 Tuttle-24, 1994 Wehner Publication,</p> <p>12 was marked for identification.)</p> <p>13 BY MR. SOILEAU:</p> <p>14 Q. It bears a JNJ Bates-numbering</p> <p>15 of 14178 through 14189. It's a Wehner 1994</p> <p>16 paper.</p> <p>17 Do you understand generally</p> <p>18 what is meant by the words "hygienic talc</p> <p>19 use"?</p> <p>20 A. I -- again, I know what I would</p> <p>21 think it would mean as hygienic talc use, but</p> <p>22 if somebody was using it, I would probably</p> <p>23 want to know what their definition was when</p> <p>24 they used it. I wouldn't want to assume my</p>

63 (Pages 246 to 249)



Kelly Tuttle, Ph.D.

<p style="text-align: right;">Page 250</p> <p>1 definition.</p> <p>2 Q. What's your understanding? I</p> <p>3 mean, you're here as an expert witness for</p> <p>4 Johnson &amp; Johnson on these talcum powder</p> <p>5 products. What's your understanding of</p> <p>6 hygienic use, hygienic talc use?</p> <p>7 A. That would be -- again, my</p> <p>8 understanding and I would have to see how it</p> <p>9 was used in context, but for personal hygiene</p> <p>10 purposes.</p> <p>11 Q. Does that mean application to</p> <p>12 the genital area?</p> <p>13 MR. FROST: Objection.</p> <p>14 A. Again, I would have to see the</p> <p>15 context in which it was being used.</p> <p>16 BY MR. SOILEAU:</p> <p>17 Q. Okay. And you do not know who</p> <p>18 A.P. Wehner is, as you now look at what I</p> <p>19 have marked as Tuttle Exhibit 24?</p> <p>20 A. Again, I'm not familiar with</p> <p>21 the name off the top of my head.</p> <p>22 Q. Okay. You see that this is a</p> <p>23 1994 paper from Wehner entitled Biological</p> <p>24 effects of cosmetic talc?</p>	<p style="text-align: right;">Page 252</p> <p>1 those are through the PubMed, Google Scholar,</p> <p>2 you know, scientific literature searches that</p> <p>3 we discussed previously.</p> <p>4 Q. Let's look at -- well, first I</p> <p>5 should be clear.</p> <p>6 Is this paper, the Biological</p> <p>7 effects of cosmetic talc, from 1994, the same</p> <p>8 paper I now have marked as Tuttle Exhibit 24,</p> <p>9 one of the four papers that you cite in your</p> <p>10 reference materials attached to your report?</p> <p>11 A. Yes, it is.</p> <p>12 Q. Okay. And doesn't Wehner</p> <p>13 address the presence of large numbers of talc</p> <p>14 particles in normal and diseased ovarian</p> <p>15 tissue in this paper, or do you know?</p> <p>16 A. Again, I would need to</p> <p>17 refamiliarize myself with this report. It</p> <p>18 does appear to be a review article. If you</p> <p>19 can refer me to that specific area you're</p> <p>20 discussing, I can flip to it.</p> <p>21 Q. Sure. Let's look at the</p> <p>22 discussion which begins on page 1181 of the</p> <p>23 paper. You see the heading Hygienic talc use</p> <p>24 and ovarian cancer?</p>
<p style="text-align: right;">Page 251</p> <p>1 A. Yes, I see that.</p> <p>2 Q. Do you know if A.P. Wehner has</p> <p>3 any association with Johnson &amp; Johnson or any</p> <p>4 connection to Johnson &amp; Johnson?</p> <p>5 MR. FROST: Objection.</p> <p>6 A. I don't know.</p> <p>7 BY MR. SOILEAU:</p> <p>8 Q. Do you know if you cited any</p> <p>9 papers by A.P. Wehner in your reference</p> <p>10 materials?</p> <p>11 A. I'd need to go to the reference</p> <p>12 section of my report and look.</p> <p>13 Q. Take a look and see if you see</p> <p>14 about four there.</p> <p>15 A. Thank you.</p> <p>16 Q. Would that surprise you?</p> <p>17 W-E-H-N-E-R.</p> <p>18 A. Thank you. I -- yes, I do cite</p> <p>19 one two, three, four A.P. Wehner reports in</p> <p>20 my reference materials.</p> <p>21 Q. Do you know how you came to</p> <p>22 have those four reports?</p> <p>23 A. Again, I know how I came to</p> <p>24 find all of the reports that I cite, and</p>	<p style="text-align: right;">Page 253</p> <p>1 A. Yes.</p> <p>2 Q. If you could follow along: The</p> <p>3 presence of large numbers of talc particles</p> <p>4 in normal and diseased ovarian tissue seems</p> <p>5 indisputable. Although it is difficult to</p> <p>6 imagine how inanimate particles without</p> <p>7 locomotion of their own can breach the</p> <p>8 formidable cervical barrier and migrate</p> <p>9 upstream -- upstream is in quotes -- against</p> <p>10 the ciliary beat of the fallopian epithelium</p> <p>11 to the ovaries.</p> <p>12 I read that sentence correctly?</p> <p>13 A. Yes, you read that sentence</p> <p>14 correctly. Again, it's one sentence out of</p> <p>15 this whole paragraph.</p> <p>16 Q. But now I'm using a paper that</p> <p>17 you cited and relied upon. This paper is not</p> <p>18 new to you?</p> <p>19 A. Correct. Again, I cite a lot</p> <p>20 of different articles. As I mentioned</p> <p>21 before, I read them all, but it's a large</p> <p>22 number of articles. I unfortunately do not</p> <p>23 have a photographic memory where I can</p> <p>24 remember everything written verbatim.</p>

64 (Pages 250 to 253)

Kelly Tuttle, Ph.D.

<p style="text-align: right;">Page 254</p> <p>1 Q. Do you consider this important 2 scientific evidence? 3 A. So -- 4 MR. FROST: Objection. 5 THE WITNESS: Sorry. 6 BY MR. SOILEAU: 7 Q. Well, you've talked today a 8 number of times about the body of scientific 9 evidence, so perhaps I could use your words 10 and frame my question this way. 11 Is this statement in the Wehner 12 article part of the body of evidence, 13 scientific evidence, that you have considered 14 in forming your opinions? 15 A. Well, again, I read and cited 16 this article. It is a review article, so it 17 does not do any research in and of its own. 18 There are no -- there's no datasets included 19 in this article. There's no methodology or 20 experiments that were performed by Dr. Wehner 21 in this article. 22 This is a review article that 23 is reviewing the body of science. And in 24 this particular sentence, again, there's no</p>	<p style="text-align: right;">Page 256</p> <p>1 A. And they're useful for, you 2 know, looking at a review of the literature, 3 finding articles and, you know, scientific 4 publications that have done experiments and 5 provided data points. 6 Q. So is the Wehner paper that is 7 Tuttle Exhibit 24 in or out for the body of 8 evidence that you considered, the body of 9 scientific evidence? 10 MR. FROST: Objection. 11 A. Well, again, as I said, it's a 12 reference that I referred to and that I cite 13 in my report, and looking at all of the 14 references that we -- I cite in my report and 15 the scientific data, it's looking at the body 16 as a whole of the scientific data and what 17 supports those conclusions. 18 As I said, this is a review 19 article so they're reviewing scientific 20 evidence and coming up with their opinions 21 and hypotheses, again, looking at this one 22 sentence out of context. There's no 23 references cited here. I know that later in 24 this same paragraph it discusses that the</p>
<p style="text-align: right;">Page 255</p> <p>1 citations for that particular sentence. You 2 know, and the paragraph goes on in discussing 3 epidemiological evidence and other 4 components, but... 5 Q. So did you rely on this article 6 in forming your opinions, or not? 7 A. Again, I reviewed and cited 8 this article, but there's no data in here. 9 There are references to cite. There's -- but 10 there's no experiments that were performed 11 for examination or to determine the basis for 12 that statement. And again, they don't cite 13 any references specifically here for me to 14 refer to. 15 Q. Why did you list this article 16 in your references? 17 MR. FROST: Objection. 18 A. Because again, it is a review 19 article that is titled the Biological effects 20 of cosmetic talc. I believe I probably cite 21 several review articles in the references of 22 my report. 23 BY MR. SOILEAU: 24 Q. Yes.</p>	<p style="text-align: right;">Page 257</p> <p>1 epidemiological evidence linking hygienic 2 talc use with an increased risk of ovarian 3 cancer generally is weak, is sometimes 4 inconsistent, discusses confounding 5 variables. 6 And again, these are summary 7 statements taken out of the discussion, but 8 there's no references taken, and we can't 9 just look at that one statement without 10 looking at the context of the entire 11 document. 12 And as I said for you, if you 13 go over to the next page and look at 1182 14 under Conclusion, it looks -- as they say, 15 there's no conclusive evidence in the 16 literature reviewed to indicate that cosmetic 17 talc, when used as intended, presents a 18 health hazard. 19 BY MR. SOILEAU: 20 Q. I think that answer was over 30 21 lines, Doctor, and really, I did not hear an 22 answer. 23 Is this paper part of the body 24 of evidence that you considered part of the</p>

Kelly Tuttle, Ph.D.

<p style="text-align: right;">Page 258</p> <p>1 body of scientific evidence, using your words 2 throughout your testimony today? 3 MR. FROST: Objection. 4 A. Well, again, as I said -- 5 BY MR. SOILEAU: 6 Q. If you could tell me it is, it 7 isn't or for some reason you can't tell me, 8 and then give me that long answer if you need 9 to again. But I need to know: Is it -- I'm 10 looking at that fence line. I need to know 11 if it's inside the fence or outside the 12 fence. Can you tell me? 13 MR. FROST: Objection. 14 A. Well, I'll try to simplify my 15 answer, that it's -- 16 BY MR. SOILEAU: 17 Q. It's real simple. Yes, no, in, 18 out. Go ahead. 19 MR. FROST: Objection. 20 A. In regards to the fence, as I 21 said, it's a review article that I cite in my 22 report. I certainly read it, reviewed it, as 23 I said I cited probably several review 24 articles in the report.</p>	<p style="text-align: right;">Page 260</p> <p>1 science is all about? We've got -- we've got 2 talcum powder applied to the genital area, 3 and we've got, according to Wehner, 4 indisputable evidence of large numbers of 5 talc particles in normal and diseased ovarian 6 tissue. As a scientist, we need to kind of 7 scratch our head and figure out how it's 8 getting there, don't we? 9 MR. FROST: Objection. 10 A. Well, as I said before, when we 11 were talking about just the presence of talc 12 particles, we need more information, you 13 know, we need more information on the studies 14 that they're examining. 15 When we're looking at the 16 question of perineal application of talcum 17 powder, there is no evidence to support that 18 the migration occurs externally from the body 19 into the female reproductive tract to the 20 ovaries. 21 BY MR. SOILEAU: 22 Q. No evidence. 23 A. And as I've said, you know, 24 previously, there are others who get into</p>
<p style="text-align: right;">Page 259</p> <p>1 So as far as being in the 2 scientific literature, yes, but this does not 3 produce any experiments or new datasets. It 4 merely is also reviewing the scientific 5 literature. 6 Q. You think Wehner knew what he 7 was talking about? 8 MR. FROST: Objection. 9 A. As I don't know Dr. Wehner... 10 BY MR. SOILEAU: 11 Q. Doesn't it kind of remind you 12 of the Hill statement when he says: It's 13 difficult to imagine how inanimate particles 14 without locomotion of their own can breach 15 the formidable cervical barrier, yet it's 16 there? 17 Do you recall the statement by 18 Hill, the Holmes/Watson statement, when you 19 rule out the impossible, the improbable 20 remains? 21 MR. FROST: Objection. Is that 22 a question? 23 BY MR. SOILEAU: 24 Q. Sure. I mean, isn't this what</p>	<p style="text-align: right;">Page 261</p> <p>1 much more detail regarding the scientific 2 literature regarding that hypothetic 3 mechanism and the science regarding it. 4 But here again, we're talking 5 about just the presence with no additional 6 context regarding where that presence is 7 found, what the studies are, what the context 8 is. 9 Q. Let's look at Exhibit 25. Do 10 you know who John Hopkins is, Dr. John 11 Hopkins? 12 (Whereupon, Deposition Exhibit 13 Tuttle-25, 3/17/97 Wehner Letter, was 14 marked for identification.) 15 A. I don't know Dr. John Hopkins 16 personally, but yes, I know who Dr. John 17 Hopkins is. 18 BY MR. SOILEAU: 19 Q. Okay. Have you seen this 20 letter that I've marked as Tuttle Exhibit 25 21 before? 22 A. No, I have not. 23 Q. Do you know who CTFA is? 24 A. No, I'm not familiar with that</p>

Kelly Tuttle, Ph.D.

<p style="text-align: right;">Page 262</p> <p>1 acronym.</p> <p>2 Q. Okay. That hasn't come up at</p> <p>3 any point during your work on this project?</p> <p>4 A. Not -- as I said, it doesn't --</p> <p>5 if it has, I -- yeah, I'm not super familiar</p> <p>6 with it, so I don't know what the acronym</p> <p>7 stands for. I apologize.</p> <p>8 Q. That's okay.</p> <p>9 You see at the top we have sort</p> <p>10 of a header for Alfred P. Wehner, Diplome,</p> <p>11 Academy of Toxicological Science?</p> <p>12 You see that?</p> <p>13 A. Yes, I see that.</p> <p>14 Q. Do you know what that is,</p> <p>15 Diplome, Academy of Toxicological Science?</p> <p>16 A. Judging from the context here,</p> <p>17 it would seem he has a diploma from the</p> <p>18 Academy of Toxicological Sciences, but I'm --</p> <p>19 I'm not familiar specifically what that</p> <p>20 means.</p> <p>21 Q. Okay. Let's look at the</p> <p>22 beginning of this letter. He says: A</p> <p>23 postscriptum to my comment faxed to you on</p> <p>24 March 16th. The date of this letter is</p>	<p style="text-align: right;">Page 264</p> <p>1 unfamiliar with.</p> <p>2 BY MR. SOILEAU:</p> <p>3 Q. Right.</p> <p>4 A. This is a postscript to</p> <p>5 apparently some previous communications. I</p> <p>6 can't really speak to this without knowing</p> <p>7 more information.</p> <p>8 Q. I'm simply asking you if this</p> <p>9 statement is consistent with your position,</p> <p>10 your opinions in this litigation, that is,</p> <p>11 that the scientific evidence did not</p> <p>12 demonstrate any real association between talc</p> <p>13 use in consumer products and ovarian tumors.</p> <p>14 Isn't that what you're telling</p> <p>15 us today?</p> <p>16 MR. FROST: Objection.</p> <p>17 A. Well, as I've said previously,</p> <p>18 it's not my opinion. The scientific evidence</p> <p>19 does not establish a causal association</p> <p>20 between talcum powder exposure perineally and</p> <p>21 ovarian cancer.</p> <p>22 BY MR. SOILEAU:</p> <p>23 Q. So you have not formed an</p> <p>24 independent expert opinion that the evidence</p>
<p style="text-align: right;">Page 263</p> <p>1 March 17, 1997.</p> <p>2 Quote, The CTFA response</p> <p>3 statement of March 10 states in its last</p> <p>4 sentence of its last full paragraph: "The</p> <p>5 determination of this workshop was that the</p> <p>6 scientific evidence did not demonstrate any</p> <p>7 real association between talc use in consumer</p> <p>8 products and ovarian tumors."</p> <p>9 I read that correctly, didn't</p> <p>10 I, Doctor?</p> <p>11 MR. FROST: Objection.</p> <p>12 BY MR. SOILEAU:</p> <p>13 Q. I know I stopped without</p> <p>14 reading the whole letter, but I read that</p> <p>15 part correctly?</p> <p>16 A. Yes, I believe so, yes.</p> <p>17 Q. And that statement in quotes,</p> <p>18 the determination of this workshop statement,</p> <p>19 that's consistent with what you're telling us</p> <p>20 today in your opinions and your testimony in</p> <p>21 this case?</p> <p>22 MR. FROST: Objection.</p> <p>23 A. Again, you know, this is in</p> <p>24 quotations. It's citing something that I'm</p>	<p style="text-align: right;">Page 265</p> <p>1 does or does not support a causal</p> <p>2 relationship?</p> <p>3 MR. FROST: Objection.</p> <p>4 A. Again, as I said, it's not my</p> <p>5 opinion. The scientific evidence is the</p> <p>6 scientific evidence, and it does not</p> <p>7 establish a causal association.</p> <p>8 BY MR. SOILEAU:</p> <p>9 Q. So are you telling me that you</p> <p>10 have, through your work in this case, simply</p> <p>11 gathered scientific information and that the</p> <p>12 scientific information, the body of</p> <p>13 scientific evidence that you have gathered,</p> <p>14 does not support a causal relationship,</p> <p>15 period?</p> <p>16 MR. FROST: Objection.</p> <p>17 A. As I said before, I have</p> <p>18 assessed scientific literature and looked at</p> <p>19 the scientific evidence, and through the</p> <p>20 context of the methodologies that we've</p> <p>21 previously discussed and that are listed in</p> <p>22 my report, the scientific evidence does not</p> <p>23 support a causal association between perineal</p> <p>24 talcum powder exposure and ovarian cancer.</p>

67 (Pages 262 to 265)

Kelly Tuttle, Ph.D.

<p style="text-align: right;">Page 266</p> <p>1 BY MR. SOILEAU:</p> <p>2 Q. I'm not a scientist, but when I</p> <p>3 hear someone say I've assessed the scientific</p> <p>4 literature, looked at the evidence and used</p> <p>5 methodologies, it sounds like they're forming</p> <p>6 an opinion.</p> <p>7 MR. FROST: Objection.</p> <p>8 BY MR. SOILEAU:</p> <p>9 Q. Did you reach an independent</p> <p>10 opinion in this case or not?</p> <p>11 MR. FROST: Objection.</p> <p>12 A. Well, again, as I said, the</p> <p>13 science doesn't support a causal association.</p> <p>14 BY MR. SOILEAU:</p> <p>15 Q. It sounds like you're telling</p> <p>16 me the science is what the science is and</p> <p>17 there's no room for opinion.</p> <p>18 MR. FROST: Objection.</p> <p>19 BY MR. SOILEAU:</p> <p>20 Q. Is that -- do I have it right</p> <p>21 now?</p> <p>22 A. Well, again, as I said -- yes,</p> <p>23 the science is the science. The science does</p> <p>24 not change when you're looking at the body of</p>	<p style="text-align: right;">Page 268</p> <p>1 scientific literature and applying the</p> <p>2 methodology, but essentially, it is what the</p> <p>3 science shows or the data supports when you</p> <p>4 look at the method, you know, when you apply</p> <p>5 the methodology, again, as put forward again</p> <p>6 in the scientific literature.</p> <p>7 Q. Doctor, in that process you</p> <p>8 just described for me, is there any part that</p> <p>9 is subjective opinion?</p> <p>10 MR. FROST: Objection.</p> <p>11 A. Again, it's an evaluation of</p> <p>12 the body of science and the application of</p> <p>13 the scientific methodology. It's what the</p> <p>14 scientific evidence says, what the scientific</p> <p>15 evidence supports or doesn't support in the</p> <p>16 case of here, and again, the scientific</p> <p>17 evidence does not support a causal</p> <p>18 association between talcum powder exposure</p> <p>19 perineally and ovarian cancer.</p> <p>20 BY MR. SOILEAU:</p> <p>21 Q. I've very clearly heard you</p> <p>22 tell me that over and over, but I need you to</p> <p>23 answer my question, and that is: Does this</p> <p>24 process, this evaluation of the body of</p>
<p style="text-align: right;">Page 267</p> <p>1 science, and when you apply the methodologies</p> <p>2 as put forward in the scientific literature,</p> <p>3 there is no causal association.</p> <p>4 BY MR. SOILEAU:</p> <p>5 Q. So, therefore, it does not</p> <p>6 require an opinion on your part, simply a</p> <p>7 matter of gathering, assessing scientific</p> <p>8 evidence and applying the methodology to</p> <p>9 arrive at the answer.</p> <p>10 Do I have it correct now?</p> <p>11 MR. FROST: Objection.</p> <p>12 A. Again, as I said, it's not</p> <p>13 about my opinion. It is about the</p> <p>14 application of the scientific methodologies</p> <p>15 as put forward in the scientific literature</p> <p>16 and the body of science, and the body of</p> <p>17 science does not support a causal</p> <p>18 association.</p> <p>19 BY MR. SOILEAU:</p> <p>20 Q. And you've come to that point,</p> <p>21 to that conclusion without injecting any</p> <p>22 opinion on your part, correct?</p> <p>23 A. Again, I use my training and</p> <p>24 expertise as a toxicologist in reviewing the</p>	<p style="text-align: right;">Page 269</p> <p>1 science, the application of scientific</p> <p>2 methodology, does it include any subjective</p> <p>3 opinion that you bring to the process?</p> <p>4 MR. FROST: Objection.</p> <p>5 A. And again, you know, it's using</p> <p>6 scientifically validated methods, scientific</p> <p>7 data, to see what the science supports, what</p> <p>8 the scientific data points to.</p> <p>9 As I said before, it's not</p> <p>10 about my opinions. It's about what the</p> <p>11 scientific evidence shows.</p> <p>12 BY MR. SOILEAU:</p> <p>13 Q. Is that a no?</p> <p>14 MR. FROST: Objection.</p> <p>15 A. I'm trying to be clear, and I'm</p> <p>16 sorry, I guess I'm not being. But it's not</p> <p>17 about my personal opinions. It's not about</p> <p>18 the opinions. It's about the scientific data</p> <p>19 and what the body of science shows.</p> <p>20 BY MR. SOILEAU:</p> <p>21 Q. So there is no part of that</p> <p>22 process that is opinion?</p> <p>23 MR. FROST: Objection.</p> <p>24 ///</p>

68 (Pages 266 to 269)



Kelly Tuttle, Ph.D.

Page 270	Page 272
<p>1 BY MR. SOILEAU: 2 Q. Do I have it right now? 3 A. Again, I -- you're -- as I 4 said, I used my training and expertise and my 5 training in toxicology to look at the 6 scientific evidence, but again, it's what the 7 evidence shows. 8 Q. Right. And only what the 9 evidence shows. 10 A. Yes. Again, it's based on the 11 body of science and the scientific evidence 12 and using scientifically -- methodologies 13 that are put forward in the scientific 14 literature. 15 Q. And no part of that process 16 includes your own personal opinions, whether 17 based on training, education, or experience 18 or not; it's the collection of the data, 19 assessing the data and applying the 20 methodology, not injecting opinion. 21 Do I have it correct? 22 MR. FROST: Objection. 23 A. Well, again, I think I stated 24 earlier, my training and expertise in</p>	<p>1 discussed this also earlier, you know, as 2 scientists, when you look at a body of 3 science and you apply a certain methodology, 4 there -- your conclusions or what the science 5 shows should be the same because the body of 6 science is not changing between individual 7 scientists. 8 BY MR. SOILEAU: 9 Q. Do you agree with the statement 10 in Tuttle Exhibit 25 that the scientific 11 evidence does not demonstrate any 12 association, any real association between 13 talc use in consumer products and ovarian 14 tumors? 15 MR. FROST: Objection. 16 A. Well, again, this is a 17 quotation. There's -- I don't know the -- 18 you know, I'm not familiar with this CTFA 19 response statement or the data it uses for 20 these determinations. This is a postscript 21 to some previous comments. 22 Without the context of this 23 statement, you know, regardless of what it 24 states, I can't agree or disagree. I -- this</p>
Page 271	Page 273
<p>1 toxicology are involved in how I assessed the 2 scientific evidence. 3 As far as I am a toxicologist, 4 I do toxicological research, and I research 5 the methods and all the things that are cited 6 in my report. 7 But ultimately, it's taking the 8 scientifically validated methods, the methods 9 established in the scientific literature, 10 applying that to the scientific literature 11 and the body of science and seeing what the 12 science supports and what the scientific 13 evidence shows. 14 BY MR. SOILEAU: 15 Q. When I make gumbo I use all the 16 ingredients people use, but it's my opinion, 17 my subjective opinion that determines when 18 it's been browned enough. 19 You see the difference? 20 MR. FROST: Objection. 21 BY MR. SOILEAU: 22 Q. It's not just the ingredients. 23 MR. FROST: Objection. 24 A. Well, again -- and I think we</p>	<p>1 is taken out of context, and again, I haven't 2 seen this before or the CTFA response. 3 BY MR. SOILEAU: 4 Q. I hear what you're saying about 5 the CTFA, the document, the folks referenced 6 in here in the details. I really want to 7 step away from that. So what I've done is 8 I've just made a statement that is not 9 referenced anywhere. It's -- I've marked it 10 as Tuttle Exhibit 26. 11 (Whereupon, Deposition Exhibit 12 Tuttle-26, Handwritten Statement, was 13 marked for identification.) 14 BY MR. SOILEAU: 15 Q. And it simply says -- can you 16 read it for me? Because that's the only copy 17 I have. 18 MR. FROST: Before we get to 19 that, I'm going to object to the use 20 of any sort of handwritten statements 21 where you're then asking our witness 22 to check agree or disagree after 23 something's written down. 24 MR. SOILEAU: Well, she doesn't</p>

69 (Pages 270 to 273)

Kelly Tuttle, Ph.D.

<p style="text-align: right;">Page 274</p> <p>1 have to check it, but I'm just trying</p> <p>2 to make the point of what the question</p> <p>3 is asking.</p> <p>4 BY MR. SOILEAU:</p> <p>5 Q. Could you read the body of the</p> <p>6 statement on that page, Tuttle Exhibit 26?</p> <p>7 A. So the statement written is:</p> <p>8 Scientific evidence demonstrates an</p> <p>9 association between talc use in consumer</p> <p>10 products and ovarian tumors.</p> <p>11 And then there is the options</p> <p>12 written below it to agree or disagree.</p> <p>13 Q. And do you -- can you agree or</p> <p>14 disagree with that statement, or you do not</p> <p>15 know?</p> <p>16 MR. FROST: Objection.</p> <p>17 A. Well, again -- and this goes</p> <p>18 back to what we're just discussing. This is</p> <p>19 a statement that you've written on a sheet of</p> <p>20 paper. There's no context. There's no data,</p> <p>21 there's no information for me to look at or</p> <p>22 examine. You know, you've been discussing</p> <p>23 the body of science.</p> <p>24 You know, I can't agree or</p>	<p style="text-align: right;">Page 276</p> <p>1 BY MR. SOILEAU:</p> <p>2 Q. And that's what's written on</p> <p>3 Tuttle Exhibit 26, isn't it, scientific</p> <p>4 evidence demonstrates?</p> <p>5 MR. FROST: Objection,</p> <p>6 misstates the document.</p> <p>7 BY MR. SOILEAU:</p> <p>8 Q. What's it say?</p> <p>9 A. Again, it says: Scientific</p> <p>10 evidence demonstrates an association between</p> <p>11 talc use in consumer products and ovarian</p> <p>12 tumors.</p> <p>13 Q. I've got approximately</p> <p>14 255 hours for you if I've deciphered the</p> <p>15 hourly rate correctly. I mean, you've done a</p> <p>16 lot of work looking at this issue.</p> <p>17 Are you prepared as we sit here</p> <p>18 today at your deposition to say that you</p> <p>19 agree or disagree with that statement on</p> <p>20 Tuttle Exhibit 26?</p> <p>21 MR. FROST: Objection.</p> <p>22 BY MR. SOILEAU:</p> <p>23 Q. If you cannot, tell me that,</p> <p>24 but I need to know if you're in a position</p>
<p style="text-align: right;">Page 275</p> <p>1 disagree with just a statement written on a</p> <p>2 piece of paper with no additional information</p> <p>3 or context.</p> <p>4 BY MR. SOILEAU:</p> <p>5 Q. Do you know how many hours you</p> <p>6 have billed for your work on behalf of</p> <p>7 Johnson &amp; Johnson in this project?</p> <p>8 A. I don't know an exact number.</p> <p>9 I think I've billed probably around 250 to</p> <p>10 300 hours.</p> <p>11 Q. So you say I can't disagree --</p> <p>12 wait a minute. Let me get your words</p> <p>13 correct.</p> <p>14 I can't agree or disagree with</p> <p>15 just a statement written on a piece of paper</p> <p>16 with no additional information or context,</p> <p>17 but you've got hundreds of hours spent</p> <p>18 studying this very issue, right?</p> <p>19 MR. FROST: Objection.</p> <p>20 A. Again, I have been assessing</p> <p>21 the scientific literature regarding, you</p> <p>22 know, whether it supports a causal</p> <p>23 association between perineal talcum powder</p> <p>24 use and ovarian cancer.</p>	<p style="text-align: right;">Page 277</p> <p>1 that allows you to agree or disagree. We can</p> <p>2 talk about why or why not in the time we have</p> <p>3 left.</p> <p>4 MR. FROST: Objection.</p> <p>5 A. Well, again, as I said, you</p> <p>6 know, I looked at the scientific evidence.</p> <p>7 In fact, we said this several times. In all</p> <p>8 of these articles, in all of these agency</p> <p>9 reports and anything that I cite in my</p> <p>10 review, you know, any statement that's made</p> <p>11 that's something of this nature, I would want</p> <p>12 to see the data behind that assumption</p> <p>13 because it's about the scientific data, not</p> <p>14 about the conclusions or assumptions of, you</p> <p>15 know, in any one article or any one</p> <p>16 handwritten document about the data and what</p> <p>17 the data supports or doesn't support.</p> <p>18 BY MR. SOILEAU:</p> <p>19 Q. Yes, Doctor, but right now the</p> <p>20 intent of my question is not about that</p> <p>21 handwritten document or the data. It's about</p> <p>22 your opinion. And I want to know your</p> <p>23 opinion. This is my chance to talk to you.</p> <p>24 Do you have an opinion to</p>

70 (Pages 274 to 277)

Kelly Tuttle, Ph.D.

<p style="text-align: right;">Page 278</p> <p>1 offer?</p> <p>2 MR. FROST: Objection.</p> <p>3 A. Again, the opinions and data</p> <p>4 that I provide are summarized in my report,</p> <p>5 and regarding this handwritten statement,</p> <p>6 again, you know, I -- as it's written on this</p> <p>7 sheet of paper, I can't agree or disagree.</p> <p>8 BY MR. SOILEAU:</p> <p>9 Q. Okay. Now, in Tuttle</p> <p>10 Exhibit 25, the statement says that the</p> <p>11 scientific evidence did not demonstrate any</p> <p>12 real association, so that's sort of the</p> <p>13 opposite of what I wrote on Tuttle</p> <p>14 Exhibit 26, right? We can at least agree on</p> <p>15 that.</p> <p>16 One says demonstrate, one says</p> <p>17 did not demonstrate, fair?</p> <p>18 A. Yes, that's fair.</p> <p>19 Q. Now, what does Alfred P.</p> <p>20 Wehner say about that --</p> <p>21 MR. FROST: Objection.</p> <p>22 BY MR. SOILEAU:</p> <p>23 Q. -- in Tuttle Exhibit 25?</p> <p>24 A. I'm sorry, can you --</p>	<p style="text-align: right;">Page 280</p> <p>1 Exhibit 27.</p> <p>2 (Whereupon, Deposition Exhibit</p> <p>3 Tuttle-27, 9/17/97 Wehner Letter, was</p> <p>4 marked for identification.)</p> <p>5 THE WITNESS: If I may, I think</p> <p>6 we're again getting close to time that</p> <p>7 I will need to take an extended break.</p> <p>8 MR. SOILEAU: Do we have time</p> <p>9 to take a quick look at Exhibit 27 or</p> <p>10 not?</p> <p>11 THE WITNESS: What time did we</p> <p>12 start?</p> <p>13 MR. FROST: I don't actually</p> <p>14 remember.</p> <p>15 THE VIDEOGRAPHER: We've been</p> <p>16 going 38 minutes.</p> <p>17 THE WITNESS: 38? Okay. Yeah,</p> <p>18 we can go a few more minutes.</p> <p>19 MR. SOILEAU: Okay. Thank you.</p> <p>20 BY MR. SOILEAU:</p> <p>21 Q. Have you seen this before, the</p> <p>22 document marked as Tuttle Exhibit 27?</p> <p>23 A. No, I have not.</p> <p>24 Q. Let me sort of guide you to a</p>
<p style="text-align: right;">Page 279</p> <p>1 Q. Help you?</p> <p>2 A. What do you mean by what does</p> <p>3 he say by that?</p> <p>4 Q. Well, doesn't Alfred P. Wehner</p> <p>5 say this statement, the statement about the</p> <p>6 determination of the workshop was that</p> <p>7 scientific evidence did not demonstrate any</p> <p>8 real association. He says this statement is</p> <p>9 technically and factually incorrect, doesn't</p> <p>10 he?</p> <p>11 A. Yes, that's what's stated, and</p> <p>12 he goes on to specify later in the</p> <p>13 postscript, he says: In summary, yes, there</p> <p>14 are those studies showing a weak association,</p> <p>15 but their biological significance is</p> <p>16 questionable for several reasons as</p> <p>17 repeatedly outlined. The data are</p> <p>18 inconsistent and therefore inconclusive.</p> <p>19 None of the authors claims to have</p> <p>20 demonstrated causality.</p> <p>21 And again, it continues on with</p> <p>22 the rest of his letter.</p> <p>23 Q. Let's look at one or two more</p> <p>24 before we move on. This is marked as Tuttle</p>	<p style="text-align: right;">Page 281</p> <p>1 place. You see he begins with an old German</p> <p>2 saying, and then there's a paragraph. Down</p> <p>3 in this paragraph it says: Several</p> <p>4 investigators have independently reported</p> <p>5 talc particles in ovarian tissue.</p> <p>6 It goes on to say: Simply</p> <p>7 citing the Battelle study and stating that it</p> <p>8 demonstrated that talc does not translate --</p> <p>9 open paren, sic, exclamation, close paren --</p> <p>10 through the cervix to the uterine cavity and</p> <p>11 beyond does not address the problem, does not</p> <p>12 refute these findings, and therefore does not</p> <p>13 serve CTFA's best interest.</p> <p>14 Do you see that?</p> <p>15 A. Yes, I see that. Again, we're</p> <p>16 looking at what appears to be some personal</p> <p>17 correspondence.</p> <p>18 Q. Okay. You see it's addressed</p> <p>19 to someone who is, at least according to this</p> <p>20 letter, in the position of manager</p> <p>21 preclinical toxicology with J&amp;J Consumer</p> <p>22 Products?</p> <p>23 A. Yes, I see that.</p> <p>24 Q. All right. And the letter is</p>

71 (Pages 278 to 281)

Kelly Tuttle, Ph.D.

<p style="text-align: right;">Page 282</p> <p>1 dated September 17, 1997?</p> <p>2 A. Yes, it is.</p> <p>3 Q. And then if you look on page 2</p> <p>4 at the first -- well, the second paragraph,</p> <p>5 we see a similar statement to what we talked</p> <p>6 about in the last exhibit from Wehner. It</p> <p>7 says, starting: The response statement dated</p> <p>8 November 17, 1994 is just as bad. The second</p> <p>9 sentence in the third paragraph reads: "The</p> <p>10 workshop concluded that, although some of</p> <p>11 these studies suggested a weak association</p> <p>12 might exist, when taken together, the results</p> <p>13 of the studies are insufficient to</p> <p>14 demonstrate any real association."</p> <p>15 That's a quote.</p> <p>16 And then he says: This</p> <p>17 statement is also inaccurate, to phrase it</p> <p>18 euphemistically.</p> <p>19 Again, you've not seen this,</p> <p>20 you don't know who he is?</p> <p>21 A. Correct. I have not seen this</p> <p>22 before. I'm not familiar with the CTFA and</p> <p>23 statement that they're referring to or, you</p> <p>24 know...</p>	<p style="text-align: right;">Page 284</p> <p>1 the record at 2:49 p.m.</p> <p>2 (Recess taken, 2:49 p.m. to</p> <p>3 3:35 p.m.)</p> <p>4 THE VIDEOGRAPHER: We're back</p> <p>5 on the record at 3:35 p.m.</p> <p>6 BY MR. SOILEAU:</p> <p>7 Q. Doctor, are you ready to</p> <p>8 proceed?</p> <p>9 A. Yes, I am.</p> <p>10 Q. Very well. Thank you.</p> <p>11 Let me show you what I will</p> <p>12 mark as Appendix C -- I'm sorry, that's not</p> <p>13 correct.</p> <p>14 I will mark it as Tuttle</p> <p>15 Exhibit 28. It is Appendix C to your report.</p> <p>16 I do not have a binder clip on this, so I'm</p> <p>17 going to give you the folder. Watch out,</p> <p>18 it's loose.</p> <p>19 (Whereupon, Deposition Exhibit</p> <p>20 Tuttle-28, Appendix C to Tuttle Expert</p> <p>21 Report, was marked for</p> <p>22 identification.)</p> <p>23 BY MR. SOILEAU:</p> <p>24 Q. This of course is Appendix C to</p>
<p style="text-align: right;">Page 283</p> <p>1 Q. Does this raise a red flag in</p> <p>2 your assessment of the body of scientific</p> <p>3 evidence?</p> <p>4 MR. FROST: Objection.</p> <p>5 A. Again, this is -- this is a</p> <p>6 personal correspondence that's looking at</p> <p>7 response statements of a working group.</p> <p>8 There's no data here. There's no reference.</p> <p>9 I mean, it -- as you said, it referenced a</p> <p>10 Battelle study previously, but you're</p> <p>11 jumping, taking these out of context.</p> <p>12 I -- I don't know what these</p> <p>13 letters are addressing or what the CTFA is</p> <p>14 addressing.</p> <p>15 BY MR. SOILEAU:</p> <p>16 Q. Okay. How about Battelle? Do</p> <p>17 you recognize Battelle at all?</p> <p>18 A. Again, the name sounds</p> <p>19 familiar. I'm not again able to recall</p> <p>20 anything specific.</p> <p>21 MR. SOILEAU: Okay. We can</p> <p>22 stop there and you can take the next</p> <p>23 break.</p> <p>24 THE VIDEOGRAPHER: Going off</p>	<p style="text-align: right;">Page 285</p> <p>1 your expert report in this case.</p> <p>2 A. Yes, it is.</p> <p>3 Q. Who prepared this document?</p> <p>4 A. Myself and my support team.</p> <p>5 Q. Step me through how it was</p> <p>6 prepared.</p> <p>7 A. So generally speaking, we</p> <p>8 reviewed the Imerys and J&amp;J documents as</p> <p>9 cited by Dr. Cook and Dr. Krekeler and tried</p> <p>10 to generate kind of a single table summary of</p> <p>11 those documents, ultimately culminating in a</p> <p>12 brief discussion of them in the report</p> <p>13 regarding specifically heavy metal analysis</p> <p>14 in the talcum powder samples.</p> <p>15 Q. Okay. Let's see if I can break</p> <p>16 that down into a few questions that I have.</p> <p>17 Is it correct that all of the</p> <p>18 source documents that led to the chart that</p> <p>19 is Appendix C came from Drs. Cook and</p> <p>20 Krekeler?</p> <p>21 A. Yes, I believe.</p> <p>22 Q. Did you obtain, request or</p> <p>23 gather any other documents other than</p> <p>24 documents that you had through Drs. Cook and</p>

72 (Pages 282 to 285)

Kelly Tuttle, Ph.D.

<p style="text-align: right;">Page 286</p> <p>1 Krekeler in order to be able to generate</p> <p>2 Appendix C?</p> <p>3 A. No.</p> <p>4 Q. Did you include in Appendix C</p> <p>5 all of the data available through the Cook</p> <p>6 and Krekeler documents?</p> <p>7 MR. FROST: Objection.</p> <p>8 A. I guess I'm not sure. I would</p> <p>9 need to look at all the data provided by</p> <p>10 Drs. Cook and Krekeler, compared with the</p> <p>11 documents we cite. As I said, we summarized</p> <p>12 them in regards to specific testing</p> <p>13 documents, so there may have been some they</p> <p>14 used that were used for alternative purposes</p> <p>15 that aren't included in this table. I'm not</p> <p>16 sure, because it's such a large number of</p> <p>17 documents.</p> <p>18 BY MR. SOILEAU:</p> <p>19 Q. You told me that Appendix C was</p> <p>20 prepared by you and your support team. Who</p> <p>21 took the lead in the preparation of</p> <p>22 Appendix C?</p> <p>23 A. Again, it was my document and</p> <p>24 my summary of the reports. I believe that</p>	<p style="text-align: right;">Page 288</p> <p>1 type of testing that is necessary to generate</p> <p>2 the data that we see in the table that is</p> <p>3 Appendix C?</p> <p>4 MR. FROST: Objection.</p> <p>5 A. Throughout the table there are</p> <p>6 several different methods noted, depending on</p> <p>7 the document. There's -- and some of these</p> <p>8 methods I'm familiar with, some of these</p> <p>9 methods I have had samples analyzed for.</p> <p>10 I have not done that type of</p> <p>11 analysis myself in regards to these samples,</p> <p>12 but again, there's several different methods</p> <p>13 in here, but some of them I have submitted</p> <p>14 samples of my own in the course of my work</p> <p>15 for analysis by similar methods.</p> <p>16 BY MR. SOILEAU:</p> <p>17 Q. So you have requested testing</p> <p>18 of materials at times in your work that would</p> <p>19 be of the same type of testing that we see</p> <p>20 reflected in some of these documents?</p> <p>21 A. Yes, that's correct. As I</p> <p>22 said, there's a number of methodologies, some</p> <p>23 of which I have used in my own line of work.</p> <p>24 Q. Yes, but I guess what I'm</p>
<p style="text-align: right;">Page 287</p> <p>1 Dana Cubanski assisted me with the actual</p> <p>2 generation of the table.</p> <p>3 Q. In terms of what information</p> <p>4 was to be included or not included in the</p> <p>5 table, who made that decision?</p> <p>6 A. Again, this is -- it was my</p> <p>7 table. In regards to what was included or</p> <p>8 not included, that would have been my</p> <p>9 decision.</p> <p>10 Q. And did you tell me that the</p> <p>11 primary purpose for Appendix C was to collect</p> <p>12 together in one document data that had been</p> <p>13 provided by Dr. Cook and then Dr. Krekeler?</p> <p>14 A. Again, as I recall, it was to</p> <p>15 assess some -- the testing materials</p> <p>16 regarding talcum powder. In -- you know, in</p> <p>17 these documents, there's other products</p> <p>18 beyond just the consumer product of talcum</p> <p>19 powder that are referenced by Dr. Cook and</p> <p>20 Dr. Krekeler for the intents and purposes of</p> <p>21 some of the -- specifically the tables</p> <p>22 regarding heavy metals in that portion of my</p> <p>23 report.</p> <p>24 Q. Have you ever conducted the</p>	<p style="text-align: right;">Page 289</p> <p>1 wondering, Doctor, you're not qualified to</p> <p>2 actually do the testing yourself. In other</p> <p>3 words, you request this information from</p> <p>4 someone, you receive the information and use</p> <p>5 it, but the actual performance of the test</p> <p>6 itself, is that something that falls within</p> <p>7 your qualifications?</p> <p>8 A. I have done some of these</p> <p>9 methods over the course of my Ph.D. I don't</p> <p>10 do lab work in my work at CTEH at this time.</p> <p>11 Q. You mentioned that you had a</p> <p>12 paragraph in your report that relied on</p> <p>13 Appendix C, I think. Is that at page 45?</p> <p>14 Take a look.</p> <p>15 A. Yes, I believe that is the</p> <p>16 summary table that I was referring to.</p> <p>17 Q. In the paragraph at the top of</p> <p>18 page 45 of your report, you say, quote, "In</p> <p>19 the case of crude talc ore, which had some of</p> <p>20 the highest detections for heavy metals, this</p> <p>21 is not comparable to the final product, which</p> <p>22 is processed via magnetic separation and acid</p> <p>23 washing to remove minerals and metals."</p> <p>24 What is the basis for your</p>

73 (Pages 286 to 289)



Kelly Tuttle, Ph.D.

Page 290	Page 292
<p>1 conclusion that the talc referenced in the 2 samples discussed in this paragraph had not 3 gone through the steps necessary to bring it 4 to a point to be comparable to the final 5 product? In other words, what's the basis 6 for this statement I just quoted from your 7 report at page 45?</p> <p>8 MR. FROST: Objection.</p> <p>9 A. So in the -- going through the 10 Imerys and J&amp;J documents, it was clear that 11 there was a wide variety of different 12 products that were being assessed and sampled 13 from ore materials down to baby powders.</p> <p>14 And the reason this statement 15 is there, and I cite the reference is that -- 16 and it is my understanding, and again, I 17 don't go into this in too great detail beyond 18 what you see here, but that the materials as 19 mined and the different grades do not 20 represent what is present in the final form.</p> <p>21 And in going through the 22 materials, I tried to separate out the other 23 samples that were, as I put in here, 24 historical talc drill samples, mine sludge,</p>	<p>1 I know that there are others involved in this 2 litigation that address that process and the 3 difference, you know, between mined talc and 4 talcum product in more detail than I do. I 5 didn't assess that specifically for my 6 purposes.</p> <p>7 When looking through these 8 documents, I tried to identify samples that 9 were specific for baby powder that could be 10 separated out from the other samples to look 11 at the testing regarding heavy metals.</p> <p>12 BY MR. SOILEAU:</p> <p>13 Q. Have you attempted to identify 14 the particular mines or sources for the talc 15 that is used in Johnson &amp; Johnson talcum 16 powder products?</p> <p>17 A. No, I have not.</p> <p>18 Q. Do you have any education in 19 geology?</p> <p>20 A. Maybe some very cursory, but 21 not an extensive education in geology, no. 22 I'm not a geologist.</p> <p>23 Q. Same question about 24 mineralogist.</p>
Page 291	Page 293
<p>1 grade 66 talc and other species from samples 2 that stated baby powder or cosmetic talc.</p> <p>3 Q. What steps had yet to be 4 undertaken, in other words, what additional 5 steps would this product still have undergone 6 based on your understanding?</p> <p>7 MR. FROST: Objection.</p> <p>8 BY MR. SOILEAU:</p> <p>9 Q. What was left to do?</p> <p>10 A. As I said, I'm not versed on 11 the step-by-step process of talc 12 manufacturing. As I said, I cite this 13 reference here that discusses it. I 14 understand there is some processing that goes 15 into generating a baby powder, but I did not 16 research that in depth. I'm not versed in 17 that process.</p> <p>18 BY MR. SOILEAU:</p> <p>19 Q. What is the basis for that 20 understanding?</p> <p>21 MR. FROST: Objection.</p> <p>22 A. Well, again, I cite the Fiume 23 study here that briefly states there is a 24 process, and I'm aware there is a process and</p>	<p>1 A. I'm not a mineralogist, no.</p> <p>2 Q. Okay. We had looked at a few 3 documents from A.P. Wehner before we took our 4 break. I'm going to show you one more that 5 I've marked as Tuttle Exhibit 29.</p> <p>6 (Whereupon, Deposition Exhibit 7 Tuttle-29, 10/7/04 Wehner Letter, was 8 marked for identification.)</p> <p>9 BY MR. SOILEAU:</p> <p>10 Q. This is a two-page document. 11 It's a letter. It's addressed to Richard 12 Zazenski, Z-A-Z-E-N-S-K-I. You may recognize 13 his name from some of the other documents we 14 looked at earlier today. And it is signed by 15 Alfred P. Wehner.</p> <p>16 Do you see in the first 17 paragraph that he is referencing a copy of 18 the retrograde migration paper by Sj?sten 19 which has been added, he says, to the paper 20 by Mills on perineal talc exposure and 21 epithelial ovarian cancer risk?</p> <p>22 A. Yes, I see that.</p> <p>23 Q. I suppose you don't know if the 24 Sj?sten, S-J-O-S-T-E-N, paper referenced here</p>

Kelly Tuttle, Ph.D.

<p style="text-align: right;">Page 294</p> <p>1 in the Wehner October 7, 2004 letter is the 2 same paper I showed you today that you had 3 not seen previously? 4 A. It doesn't specify the year, 5 and again, these are personal communications 6 so I have no way to know what they're 7 discussing specifically. 8 Q. It says in part in here in the 9 third paragraph: The study generally is very 10 similar to 14 or so previous retrospective 11 case-control studies with all the inherent 12 well-discussed and published weaknesses of 13 such studies. Its ORs are well below 2.0. 14 Do you see that part of the 15 letter on the first page? 16 A. Yes, I see -- I see that part 17 of the letter. 18 Q. Do you know what an OR is? 19 A. I believe it refers to an odds 20 ratio. 21 Q. Okay. And what is the 22 significance of an odds ratio that is below 23 or well below 2.0? 24 A. In my training, odds ratios of</p>	<p style="text-align: right;">Page 296</p> <p>1 training, did not have biological 2 significance? 3 MR. FROST: Objection. 4 A. We're speaking in very broad 5 terms. You know, it depends on the science 6 and the data. You know, I'm speaking 7 generally when I say that the odds ratio of 8 2.0 is kind of what we used when doing my 9 research for my Ph.D. It's what was taught 10 in -- when analyzing scientific data. 11 BY MR. SOILEAU: 12 Q. Are we in an area that is -- 13 well, is this area comfortable to you, that 14 is, within your expertise, comfortably within 15 your expertise, when we start talking about 16 odds ratios? 17 MR. FROST: Objection. 18 A. I'm familiar with odds ratios. 19 I use odds ratios. You know, I'm familiar 20 with confidence intervals, I have training 21 and experience in them as part of my work in 22 toxicology. 23 BY MR. SOILEAU: 24 Q. Right.</p>
<p style="text-align: right;">Page 295</p> <p>1 2.0 was kind of the -- I'm trying to think of 2 the best way to describe it, is the kind of 3 established -- the level you start looking 4 for when you're performing experiments. 5 As far as 2.0, you would like 6 to see odds ratios above 2.0 in regards to 7 looking at biological impacts or potential 8 relationships. 9 Q. Does that mean that as long as 10 you are at or below 2.0 in your opinion, you 11 do not have evidence of a biological impact 12 or potential relationship? 13 A. Well, as I said, 2.0 is kind 14 of -- as I said, what I was taught and what 15 we practice in our -- in my Ph.D. training 16 and expertise as regards to when doing 17 research and doing analysis of relationships, 18 odds ratios above 2.0, you know, we kind of 19 were -- it's rather hard to describe, but 20 it's kind of the area we were looking for 21 from a point of biological significance. 22 Q. Okay. Does that mean that 23 taking the converse, that odds ratios that 24 were not above 2.0, according to your</p>	<p style="text-align: right;">Page 297</p> <p>1 The beginning of that statement 2 sort of sounded like my plumbing. I used the 3 plumbing. I'm familiar with the plumbing. I 4 can do some things, but I'm not a plumber. 5 I'm just trying to understand 6 if, you know, when we start talking about 7 odds ratios, if that is an area -- and I'm 8 going to take some letter -- I'm sorry, some 9 language from this letter where he says 10 recognized epidemiologists and statisticians. 11 I mean, is that who you would 12 point me to or is this something that you 13 feel you're well versed to discuss as an 14 expert? 15 MR. FROST: Objection. 16 BY MR. SOILEAU: 17 Q. Odds ratios, that is? 18 MR. FROST: Objection. 19 A. I guess it would depend on the 20 specific question. As I said, I have 21 training and expertise in odds ratios and 22 statistical analysis. I assess them, I use 23 them. I'm not a statistician, so if there 24 were things that we -- you know, getting into</p>

75 (Pages 294 to 297)

Kelly Tuttle, Ph.D.

<p style="text-align: right;">Page 298</p> <p>1 more detail regarding odds ratios or  2 something, I would probably refer you to  3 others that get more into the statistical  4 analysis and the methodology surrounding  5 statistical analysis.  6 BY MR. SOILEAU:  7 Q. When I asked you earlier about  8 the converse of greater than 2.0 odds ratios,  9 and I think you told me something like it's  10 going to depend on some of the context or  11 circumstances. You said you know it depends  12 on the science and the data.  13 Is that sort of one of those  14 areas where opinion comes into play, there's  15 a subjective element to assess the data and  16 decide if it is significant even though it's  17 below 2.0?  18 MR. FROST: Objection.  19 A. No, that's not what I'm saying.  20 BY MR. SOILEAU:  21 Q. Okay.  22 A. I'm saying you need to know the  23 context of the data itself to generally speak  24 to an odds ratio, regardless whether it's</p>	<p style="text-align: right;">Page 300</p> <p>1 context. When we're talking about cause  2 relationships, we always have to bring it  3 back to the Hill criteria and the nine  4 viewpoints as a whole.  5 As we said earlier, strength,  6 which would be, you know, odds ratios is  7 definitely a -- one of viewpoints of the Hill  8 criteria and one of the key viewpoints, and  9 as we talked about previously, when you're  10 looking at them, you have to look at them as  11 a whole and look at them in context when  12 you're establishing your -- whether they  13 support a causal association.  14 And odds ratio, again, you  15 know, you need to look at the context of the  16 study that developed the odds ratio, you need  17 to look at other studies also as well to look  18 at their odds ratios, and in general, look at  19 the data to -- let's see what the data  20 supports.  21 So as far as whether one  22 particular odds ratio, you know, is or is not  23 involved in causal, you have to look at the  24 entire body of science in the context of the</p>
<p style="text-align: right;">Page 299</p> <p>1 above 2.0 or below 2.0, it requires more  2 context about the science and the data.  3 Q. Based on your training, could  4 an odds ratio of 1.6 be relevant, important  5 scientific evidence on the issue of  6 causation?  7 MR. FROST: Objection.  8 A. Again, it depends.  9 BY MR. SOILEAU:  10 Q. Well, could it ever? When I  11 hear you say it depends, that means it might,  12 it might not. So I'm just trying to be  13 complete and fair. That means, yes, it could  14 be, but, no, it might not be. And that's  15 fine, but that's specifically what I'm  16 asking.  17 Is it possible? You understand  18 possible just means possible. Is it possible  19 that under the appropriate circumstances an  20 odds ratio of 1.6 could offer evidence of a  21 cause relationship?  22 MR. FROST: Objection.  23 A. Again, it would -- it would --  24 it would depend. You'd have to look at the</p>	<p style="text-align: right;">Page 301</p> <p>1 causal assessment.  2 BY MR. SOILEAU:  3 Q. So you couldn't just go, well,  4 it's 1.6 or it's 1.4, 1.5, so I'm going to  5 rule out any significance for that study?  6 You can't just out of hand do  7 it; you have to look at the data, look at the  8 study and decide what weight, if any, it's  9 entitled to, fair?  10 MR. FROST: Objection.  11 A. Again, you have to look at the  12 data and the science. You know, odds -- as I  13 said, odds ratios are useful and there's --  14 we talked about the 2.0 or below 2.0, but you  15 have to look at that as well as the  16 scientific data as a whole.  17 BY MR. SOILEAU:  18 Q. Look at the second page of  19 Exhibit 29. The middle paragraph includes a  20 statement: I would recommend to have this  21 study evaluated by a reputable epidemiologist  22 well familiar with the talc issue (e.g.,  23 Dr. Huncharek, H-U-N-C-H-A-R-E-K, comes to  24 mind).</p>

Kelly Tuttle, Ph.D.

<p style="text-align: right;">Page 302</p> <p>1 Do you recognize that name from</p> <p>2 your work in this litigation?</p> <p>3 A. Yes, I believe so.</p> <p>4 Q. How?</p> <p>5 A. I think I cite some</p> <p>6 Huncharek -- I'm not sure if I'm saying it</p> <p>7 right -- references in my report.</p> <p>8 Q. Do you want to check?</p> <p>9 A. Certainly.</p> <p>10 Q. Look at page 77, see if you see</p> <p>11 three different references.</p> <p>12 A. Yes, I do.</p> <p>13 Q. Do you know anything else about</p> <p>14 Dr. Huncharek?</p> <p>15 A. No, I don't.</p> <p>16 Q. Do you even know if he's --</p> <p>17 well, the letter says he's a doctor, but you</p> <p>18 don't even know that, I guess.</p> <p>19 A. When I look at scientific</p> <p>20 articles, I don't really research the</p> <p>21 authors. I look at the science and the data.</p> <p>22 Q. Do you look at the publication</p> <p>23 to see where it was published?</p> <p>24 A. Obviously when citing them and</p>	<p style="text-align: right;">Page 304</p> <p>1 by what you said in your report on these</p> <p>2 issues, migration?</p> <p>3 A. Yes, my report -- my report is</p> <p>4 my work, and I stand by what I write in my</p> <p>5 report, yes.</p> <p>6 Q. And nothing that we've</p> <p>7 discussed today causes you to want to pause</p> <p>8 and revisit any of your opinions or analysis</p> <p>9 of the migration issue?</p> <p>10 A. Well, as I've said before,</p> <p>11 you've -- you've shown me some personal</p> <p>12 correspondence that would have no bearing on</p> <p>13 a scientific investigation, and the articles</p> <p>14 you've provided me, I haven't had a chance to</p> <p>15 read in depth. But generally speaking, none</p> <p>16 of them looked at external perineal</p> <p>17 application and the successful migration from</p> <p>18 external application to the ovaries.</p> <p>19 Q. So you do not feel as we sit</p> <p>20 here today any need to say I'd like to</p> <p>21 revisit that issue?</p> <p>22 A. Well, as I state in my report,</p> <p>23 you know, if new evidence comes available, I</p> <p>24 always reserve the right, but based on what</p>
<p style="text-align: right;">Page 303</p> <p>1 stuff, I look at the journals where they have</p> <p>2 been published, but I don't necessarily, as</p> <p>3 far as assessing the journals themselves.</p> <p>4 Q. Do you still maintain as we sit</p> <p>5 here this afternoon that there is no</p> <p>6 scientific evidence to support the theory of</p> <p>7 migration and that Drs. Plunkett and Zelikoff</p> <p>8 were scientifically unsound and flawed in</p> <p>9 their opinions?</p> <p>10 MR. FROST: Objection,</p> <p>11 misstates testimony, misstates</p> <p>12 opinion.</p> <p>13 A. Well, again, I would refer to</p> <p>14 the opinions in my report. The scientific</p> <p>15 evidence does not support the hypothesis that</p> <p>16 external application of talcum powder can</p> <p>17 migrate through the female reproductive tract</p> <p>18 to the ovaries, and in the opinions of my</p> <p>19 report, I do not criticize Dr. Plunkett or</p> <p>20 Dr. Zelikoff. I merely am critical of the</p> <p>21 methodologies, and as I said, the scientific</p> <p>22 evidence does not support the hypotheses.</p> <p>23 BY MR. SOILEAU:</p> <p>24 Q. Does that mean that you stand</p>	<p style="text-align: right;">Page 305</p> <p>1 you've presented to me and what I have seen</p> <p>2 in the scientific evidence, there's nothing</p> <p>3 to support the proposed migration theory of</p> <p>4 external application of talcum powder</p> <p>5 migrates to the ovaries.</p> <p>6 Q. The issue of plausibility, it</p> <p>7 includes -- the plausibility under the Hill</p> <p>8 viewpoints, that includes mechanism, right?</p> <p>9 A. I -- the biological</p> <p>10 plausibility -- we can refer to the Hill to</p> <p>11 look at it distinctly, but yes, it generally</p> <p>12 refers to a proposed mechanism of exposure or</p> <p>13 of toxicity.</p> <p>14 Q. Okay. So a proposed mechanism</p> <p>15 of toxicity.</p> <p>16 What does the word "toxicity"</p> <p>17 mean?</p> <p>18 A. Of adverse health effect, how</p> <p>19 the adverse health effect is caused by a</p> <p>20 certain dose of product.</p> <p>21 Q. Okay. And will you agree that</p> <p>22 investigators have studied proposed</p> <p>23 mechanisms by which talc might initiate or</p> <p>24 contribute to a carcinogenic process?</p>

77 (Pages 302 to 305)

Kelly Tuttle, Ph.D.

<p style="text-align: right;">Page 306</p> <p>1 MR. FROST: Objection.</p> <p>2 A. I am aware there have been some</p> <p>3 mechanistic studies regarding talcum powder</p> <p>4 and ovarian cells in vitro and in vivo.</p> <p>5 BY MR. SOILEAU:</p> <p>6 Q. Well, let me ask you this: Can</p> <p>7 you agree with this statement: Investigators</p> <p>8 have studied proposed mechanisms by which</p> <p>9 talc might initiate or contribute to a</p> <p>10 carcinogenic process?</p> <p>11 MR. FROST: Objection.</p> <p>12 BY MR. SOILEAU:</p> <p>13 Q. Can you agree with that?</p> <p>14 A. Again, I'm aware that research</p> <p>15 has been done both in vitro and in vivo. I</p> <p>16 do not get into that in my report. I don't</p> <p>17 do a detailed research regarding the genetic</p> <p>18 mechanistic research regarding talcum powder</p> <p>19 and ovarian cancer.</p> <p>20 Q. Would you look at your report</p> <p>21 at page 27, please, Doctor? Do you find</p> <p>22 there a one-paragraph section numbered 7.3.3</p> <p>23 and entitled Studies on Talc, Inflammation</p> <p>24 and Ovarian Cancer?</p>	<p style="text-align: right;">Page 308</p> <p>1 taken verbatim from your report, right?</p> <p>2 MR. FROST: Objection.</p> <p>3 A. Again, it's the first half of</p> <p>4 that sentence in the paragraph discussing</p> <p>5 studies on talc, inflammation and ovarian</p> <p>6 cancer.</p> <p>7 BY MR. SOILEAU:</p> <p>8 Q. How about this: The words that</p> <p>9 I presented to you are, in fact, your words,</p> <p>10 Doctor.</p> <p>11 MR. FROST: Objection.</p> <p>12 A. Again, as I stated, that is</p> <p>13 what I've written in the first half of that</p> <p>14 sentence on that paragraph regarding on</p> <p>15 studies on talc, inflammation and ovarian</p> <p>16 cancer.</p> <p>17 BY MR. SOILEAU:</p> <p>18 Q. Right. That's why I say these</p> <p>19 words are your words, fair?</p> <p>20 MR. FROST: Objection.</p> <p>21 A. Again, that's the first half of</p> <p>22 the sentence that is written there, along</p> <p>23 with the rest of the paragraph.</p> <p>24 ///</p>
<p style="text-align: right;">Page 307</p> <p>1 A. Yes, I see it.</p> <p>2 Q. Would you read that statement,</p> <p>3 the first sentence of that paragraph into the</p> <p>4 record, please?</p> <p>5 A. Investigators have studied</p> <p>6 proposed mechanisms by which talc might</p> <p>7 initiate or contribute to a carcinogenic</p> <p>8 process, including whether talc causes</p> <p>9 inflammation or whether inflammation is</p> <p>10 itself related to the initiation of ovarian</p> <p>11 cancer.</p> <p>12 Q. So, Doctor, let me ask you</p> <p>13 again. Can you agree with this statement:</p> <p>14 Investigators have studied proposed</p> <p>15 mechanisms by which talc might initiate or</p> <p>16 contribute to a carcinogenic process?</p> <p>17 MR. FROST: Objection.</p> <p>18 A. Again, that's what I state in</p> <p>19 the first half of that sentence of my report,</p> <p>20 and as I stated previously, I'm aware that</p> <p>21 there have been in vitro and in vivo studies</p> <p>22 looking at genetic mechanisms.</p> <p>23 BY MR. SOILEAU:</p> <p>24 Q. Precisely, the statement is</p>	<p style="text-align: right;">Page 309</p> <p>1 BY MR. SOILEAU:</p> <p>2 Q. I mean, you don't suggest I</p> <p>3 have to read the whole report to you for it</p> <p>4 to be your words. I'm not saying that's the</p> <p>5 entirety of your report. I'm just saying --</p> <p>6 well, did you write those words?</p> <p>7 A. Yes, I wrote those words.</p> <p>8 Q. Okay. So they are your words?</p> <p>9 A. Again, yes, those are the words</p> <p>10 that I wrote, that is the first half of that</p> <p>11 sentence in that paragraph.</p> <p>12 Q. Well, once we get past this,</p> <p>13 I'm going to keep going on the sentence where</p> <p>14 we got hung up. Let's see if we can keep</p> <p>15 going.</p> <p>16 And when investigators have</p> <p>17 studied proposed mechanisms by which talc</p> <p>18 might initiate or contribute to a</p> <p>19 carcinogenic process, can you agree that has</p> <p>20 included whether talc causes inflammation?</p> <p>21 A. I'm sorry, can you repeat that</p> <p>22 for me?</p> <p>23 Q. Sure.</p> <p>24 A. I was -- I thought you were</p>

78 (Pages 306 to 309)



Kelly Tuttle, Ph.D.

Page 310	Page 312
<p>1 quoting my report.</p> <p>2 Q. Well, I sort of took it from</p> <p>3 your report, but I'm simply asking you if</p> <p>4 investigators who have studied proposed</p> <p>5 mechanisms by which talc might initiate or</p> <p>6 contribute to a carcinogenic process have</p> <p>7 included within those studies the question of</p> <p>8 whether talc causes inflammation?</p> <p>9 A. And again, I'm aware of studies</p> <p>10 that have looked at whether talc causes</p> <p>11 inflammation.</p> <p>12 Q. And also whether inflammation</p> <p>13 is itself related to the initiation of</p> <p>14 ovarian cancer, fair?</p> <p>15 A. Yes. Again, I'm aware that</p> <p>16 investigators have studied that.</p> <p>17 Q. You will agree with me that</p> <p>18 when large numbers of foreign particles of</p> <p>19 any composition deposit on tissue, an initial</p> <p>20 response can be irritation?</p> <p>21 MR. FROST: Objection.</p> <p>22 A. Well, you're speaking in broad</p> <p>23 strokes --</p> <p>24 ///</p>	<p>1 issues, haven't you?</p> <p>2 A. Inhalation toxicology is</p> <p>3 something we do a lot of at CTEH, yes.</p> <p>4 Q. Right. And the work that</p> <p>5 you've done on asbestos and some chemical</p> <p>6 releases that are referenced in some of the</p> <p>7 materials that I've been provided with or</p> <p>8 gathered, a lot of those involve inhalation;</p> <p>9 not suggesting that it's limited to just</p> <p>10 inhalation, but inhalation has been an issue</p> <p>11 in a lot of those projects that you've worked</p> <p>12 on?</p> <p>13 A. Yes.</p> <p>14 Q. Okay. If large numbers of</p> <p>15 foreign particles of any composition deposit</p> <p>16 in the airways, will the initial response be</p> <p>17 irritation?</p> <p>18 A. Again, it depends. Depends on</p> <p>19 the foreign particle, depends on the dose,</p> <p>20 but certainly there are circumstances where</p> <p>21 foreign bodies may deposit on the lung and</p> <p>22 cause irritation.</p> <p>23 Q. And it's possible that</p> <p>24 irritation will be followed by inflammation?</p>
Page 311	Page 313
<p>1 BY MR. SOILEAU:</p> <p>2 Q. Yes.</p> <p>3 A. -- again, and, you know, as you</p> <p>4 said, can cause inflammation. Depending on</p> <p>5 the scenario, the exposure, the particles,</p> <p>6 yes, acute inflammation can occur.</p> <p>7 Q. Well, isn't the initial</p> <p>8 response irritation?</p> <p>9 MR. FROST: Objection.</p> <p>10 A. We were just discussing</p> <p>11 inflammation, so now we jumped to irritation.</p> <p>12 Is there -- I'm afraid you're kind of -- I'm</p> <p>13 not sure how you define irritation versus</p> <p>14 inflammation.</p> <p>15 BY MR. SOILEAU:</p> <p>16 Q. Well, I was just asking, if you</p> <p>17 have a large number of foreign particles of</p> <p>18 any composition deposit on tissue, if the</p> <p>19 initial response is irritation? Go ahead. You</p> <p>20 want to answer it or you want me to rephrase</p> <p>21 it?</p> <p>22 A. I was going to say it depends.</p> <p>23 Q. Let's put it in the lungs.</p> <p>24 You've done a lot of work on inhalation</p>	<p>1 A. Again, it depends on the</p> <p>2 scenario and the dose and a number of other</p> <p>3 factors. Again, when you're talking about</p> <p>4 the lung, there are certainly conditions for</p> <p>5 which foreign bodies will deposit in the lung</p> <p>6 and cause inflammation, an acute inflammatory</p> <p>7 response.</p> <p>8 Q. Okay. And if you get an</p> <p>9 inflammatory response, are there macrophages</p> <p>10 that then play a central role?</p> <p>11 A. There are a large number of</p> <p>12 different components involved in the</p> <p>13 inflammatory process, and I have not</p> <p>14 refreshed my memory recently enough to be</p> <p>15 able to recall all of them involved.</p> <p>16 Macrophages are certainly involved.</p> <p>17 Q. Well, isn't it fair to say that</p> <p>18 the macrophages in the lungs in the</p> <p>19 respiratory system would play a central role</p> <p>20 if you had a deposition of foreign particles</p> <p>21 that triggered irritation followed by</p> <p>22 inflammation?</p> <p>23 MR. FROST: Objection.</p> <p>24 A. As I said, there's a large</p>

79 (Pages 310 to 313)

Kelly Tuttle, Ph.D.

<p style="text-align: right;">Page 314</p> <p>1 number of different cells and cytokines and 2 things involved in the inflammatory response. 3 I can't say whether macrophages play a 4 central role without refreshing my knowledge 5 about the inflammatory response and the 6 individual cells involved in it. 7 BY MR. SOILEAU: 8 Q. Earlier you spoke about defense 9 systems, I believe, in the body. Is it true 10 that different organs have different levels, 11 different degrees of defense systems? 12 A. Again, that's a very general 13 statement. As far as -- as I said 14 previously, the body has a number of 15 different defense mechanisms. 16 Q. But are the body's defense 17 mechanisms, if you know, the same for 18 different organs? For example, the same in 19 the lungs as in the kidneys as in the ovaries 20 as in the brain, or does it vary from organ 21 to organ, if you know? 22 A. Yeah, I have not done a 23 detailed assessment of the different target 24 organs' defense mechanisms. I would say that</p>	<p style="text-align: right;">Page 316</p> <p>1 A. Yes, I believe so. 2 Q. Does that involve the effect or 3 process of the macrophages in the body, if we 4 go back to our foreign particles in the 5 lungs, the macrophages' response to these 6 foreign particles in the body? 7 MR. FROST: Objection. 8 BY MR. SOILEAU: 9 Q. Is that generally what we're 10 talking about? 11 A. And again, as I said, I haven't 12 brushed up on my knowledge of the detailed -- 13 the complex inflammatory process. Phagocytosis -- 14 phagocytize, I'm sorry if I am not saying 15 1999 right, but -- 16 Q. I had to practice. 17 Phagocytize. 18 A. I don't recall and can't say 19 that it's specific to macrophages, but it 20 certainly involves the uptake of material, 21 generally speaking, into cells, and not 22 necessarily foreign bodies. It can be 23 involving other products as well. 24 Q. This process that I'm sort of</p>
<p style="text-align: right;">Page 315</p> <p>1 there are some that are the same and some 2 that vary. But we would have to kind of 3 compare -- pick two organs and actually 4 compare the defense mechanisms. 5 Q. Lungs and ovaries. 6 A. Well, again, as I said, I 7 haven't done a detailed research for every 8 defense mechanism and I said earlier that I 9 have not studied specifically the defense 10 mechanisms of the ovaries. 11 Q. Okay. Are we, from your 12 perspective, still within your area of 13 expertise? 14 MR. FROST: Objection. 15 A. Well, as I said, you know, I 16 address inflammation briefly in my report. I 17 do not get into the detailed mechanisms of 18 inflammation. As I said previously, I have 19 not researched the defense mechanisms of the 20 ovary. I don't address the defense 21 mechanisms of the ovary in my report. 22 BY MR. SOILEAU: 23 Q. Do you know what the word 24 phagocytize means?</p>	<p style="text-align: right;">Page 317</p> <p>1 stepping through here, foreign particles, 2 irritation, inflammatory responses, 3 macrophages, phagocytize, other defense 4 mechanisms, this is a process that can unfold 5 in the body when it's confronted with some 6 foreign agent. You know that as a 7 toxicologist, right? 8 MR. FROST: Objection. 9 A. Inflammation can occur in the 10 body for a number of reasons. It's a healthy 11 response in the human body beyond just 12 foreign bodies. 13 BY MR. SOILEAU: 14 Q. Right. But it can also be a 15 response to foreign particles, can it not? 16 A. Again, depending on the 17 situation and the dose and stuff, there are 18 certainly instances where foreign bodies can 19 induce acute inflammation. 20 Q. Okay. And it can trigger what 21 we would call a cascade, that is, a cascade 22 of responses and reactions within the tissue, 23 if the dose is sufficient to trigger 24 toxicity?</p>

Kelly Tuttle, Ph.D.

Page 318	Page 320
<p>1 MR. FROST: Objection.</p> <p>2 BY MR. SOILEAU:</p> <p>3 Q. The dose of the foreign</p> <p>4 particle, right?</p> <p>5 MR. FROST: Objection.</p> <p>6 A. You're getting a little out of</p> <p>7 what I cover in my report and what I have</p> <p>8 done. As I said, I haven't done a refresher</p> <p>9 course on inflammatory response. That would</p> <p>10 depend, because depending on the chemical and</p> <p>11 the exposure of issue, you know, as far as</p> <p>12 whether the inflammatory response is involved</p> <p>13 in the mechanism of toxicity.</p> <p>14 So I don't -- I can't speak to</p> <p>15 that specifically without doing some</p> <p>16 additional research, having a specific</p> <p>17 scenario.</p> <p>18 BY MR. SOILEAU:</p> <p>19 Q. Do you -- I'm sorry, I didn't</p> <p>20 mean to step over your words.</p> <p>21 Do you recognize the term</p> <p>22 "cascade," Doctor, in this context?</p> <p>23 A. Yes, but as I said, we're</p> <p>24 getting a little out of the realm of what I</p>	<p>1 Q. Generally.</p> <p>2 A. I think I --</p> <p>3 Q. Let me show you -- go ahead,</p> <p>4 I'm sorry, you have an answer?</p> <p>5 A. Yeah, I was going to say I</p> <p>6 think I have done some inflammation work in</p> <p>7 my Ph.D. I can't remember if I specifically</p> <p>8 addressed it in one of my publications or</p> <p>9 not. But as I said before, I have -- I'm</p> <p>10 aware of inflammation, but I haven't brushed</p> <p>11 up on the intricate genetic roles and all the</p> <p>12 complexities of it.</p> <p>13 Q. Let me show you an article that</p> <p>14 I read and make sure it's one that you are an</p> <p>15 author -- one of the authors of.</p> <p>16 (Whereupon, Deposition Exhibit</p> <p>17 Tuttle-30, 2014 Nony et al</p> <p>18 Publication, was marked for</p> <p>19 identification.)</p> <p>20 BY MR. SOILEAU:</p> <p>21 Q. I've marked it as Tuttle</p> <p>22 Exhibit 30. Do you recognize this article?</p> <p>23 A. Yes, I do.</p> <p>24 Q. Are you, in fact, one of the</p>
Page 319	Page 321
<p>1 discuss in my opinions.</p> <p>2 Q. In some scenarios -- I</p> <p>3 understand that. You do have a section on</p> <p>4 inflammation and talc, but you haven't</p> <p>5 discussed some of these issues that I'm</p> <p>6 bringing up that center upon the body's</p> <p>7 response to foreign particles and</p> <p>8 inflammation and this cascade, fair?</p> <p>9 MR. FROST: Objection.</p> <p>10 BY MR. SOILEAU:</p> <p>11 Q. That's what you're telling me</p> <p>12 right?</p> <p>13 A. Again, yes. As I said, you're</p> <p>14 discussing the cascades and the intricate</p> <p>15 mechanisms of the inflammatory responses is</p> <p>16 not something that I do in my report and not</p> <p>17 something that I research in depth in my</p> <p>18 report. I believe there are others who get</p> <p>19 more into the mechanisms and pathways</p> <p>20 regarding inflammation than I do.</p> <p>21 Q. Well, is it something that</p> <p>22 you've written on?</p> <p>23 A. You mean in my report, or do</p> <p>24 you mean generally or --</p>	<p>1 three authors of this article?</p> <p>2 A. I am.</p> <p>3 Q. Would you turn to page 2,</p> <p>4 Mechanisms of Toxicity? You see it?</p> <p>5 A. Yes.</p> <p>6 Q. It does say: When large</p> <p>7 numbers of foreign particles of any</p> <p>8 composition deposit in the airways or the</p> <p>9 bronchial alveolar region of the lung, the</p> <p>10 initial response is irritation. Doesn't it?</p> <p>11 A. Yes, that's what it states</p> <p>12 right here, it says the initial response is</p> <p>13 irritation followed by inflammation.</p> <p>14 Q. And it says: Followed by</p> <p>15 inflammation in which the AMs, that's capital</p> <p>16 A, capital M, little s, play a central role.</p> <p>17 Do you know what the AMs are there?</p> <p>18 A. If I remember correctly, and</p> <p>19 I'm sure we probably elucidated earlier, I</p> <p>20 believe it refers to activated macrophages.</p> <p>21 Q. Okay. It could be -- I can't</p> <p>22 say the word very well. Alveolar?</p> <p>23 A. Alveolar?</p> <p>24 Q. I tell you what. Go up to the</p>

81 (Pages 318 to 321)

Kelly Tuttle, Ph.D.

<p style="text-align: right;">Page 322</p> <p>1 paragraph before, right in the middle, and 2 let me show you on the screen. You see right 3 here? 4 MR. SOILEAU: Oops. 5 (Comments off the stenographic 6 record.) 7 BY MR. SOILEAU: 8 Q. So what does AM stand for? 9 A. Alveolar macrophages. 10 Q. Alveolar, thank you. Now I can 11 say it correctly. 12 And then it goes on to say, 13 still under Mechanisms of Toxicity near the 14 bottom of the page: The AMs migrate to sites 15 of dust deposition and attempt to phagocytize 16 the particles, destroy them or translocate 17 them to the -- what's that word? 18 A. Mucociliary. 19 Q. Escalator. 20 What does that mean? 21 A. So it's one of the defense 22 mechanisms that we were discussing, and 23 again, it's been a few years since this was 24 drafted, so I will try to speak accurately.</p>	<p style="text-align: right;">Page 324</p> <p>1 secretion to generate -- generation of 2 reactive oxygen species (ROS), and release of 3 inflammatory mediators. 4 What are reactive oxygen 5 species? 6 A. So I don't know that I can 7 really define that very clearly just, as I 8 said, off the cuff. You know, reactive 9 oxygen species, you know, I probably prefer 10 to refer to a definition in front of me to 11 make sure I'm speaking accurately regarding 12 them. 13 Q. Okay. Do you know if reactive 14 oxygen species are significant to the 15 carcinogenic process? 16 MR. FROST: Objection. 17 A. It would depend. I have not 18 done a specific assessment of that in this 19 case, and it would depend. I'd need more 20 information or I'd need to be able to 21 research that. 22 BY MR. SOILEAU: 23 Q. Let's look at the last 24 sentence: The cascade continues as long as</p>
<p style="text-align: right;">Page 323</p> <p>1 Q. Okay. 2 A. But when you think of -- to put 3 it in layman's terms, coughing up a loogie. 4 Q. Okay. Right. This is one of 5 the things the respiratory system can do to 6 expel things that have come into it, foreign 7 things that have come into the respiratory 8 system? 9 MR. FROST: Objection. 10 BY MR. SOILEAU: 11 Q. Is that right? 12 A. Again, it's one of the defense 13 mechanisms. 14 Q. Yeah. 15 A. In this particular chapter 16 where we're referring to foreign particles, I 17 think it can also be used in other scenarios 18 within the lung as well. 19 Q. Sure. Let me finish this 20 paragraph. 21 Simultaneously, the phagocytes 22 release a complex series of chemical 23 messengers that activate and attract 24 inflammatory cells stimulating mucous</p>	<p style="text-align: right;">Page 325</p> <p>1 the irritant particles persist, subsiding 2 only when and if the particles are cleared 3 from the lung. 4 Do you agree with that 5 statement? 6 MR. FROST: Objection. 7 A. Well, again, as I said before, 8 when exposed in the lung, as I stated 9 previously, foreign particles at a sufficient 10 dose can certainly cause irritation followed 11 by inflammation. 12 As far as the cascade statement 13 in this particular context, looking at this, 14 you know, the response is there to remove 15 these foreign particles, so as long as the 16 particles are there, and then when they're 17 removed, the inflammatory response ends. 18 Cascade, again, what you asked 19 earlier involved cascade and toxicity, and 20 this is a little bit of a different scenario 21 that we're looking at in this article, just 22 the general inflammatory response. 23 BY MR. SOILEAU: 24 Q. Well, this is not discussing</p>

Kelly Tuttle, Ph.D.

<p style="text-align: right;">Page 326</p> <p>1 mechanism of toxicity in this article?</p> <p>2 A. Again, yes, this is discussing</p> <p>3 mechanism of toxicity very generally in</p> <p>4 regards to foreign particles.</p> <p>5 Q. That's what I thought. That's</p> <p>6 what I understood.</p> <p>7 Let's go back for a moment to</p> <p>8 Exhibit 23, that FDA response that we</p> <p>9 discussed earlier. I'm going back to page 5</p> <p>10 of 7. I'm revisiting language we looked at</p> <p>11 earlier.</p> <p>12 I'm going to go to the middle</p> <p>13 of that paragraph. It is, therefore,</p> <p>14 plausible that perineal talc (and other</p> <p>15 particulate) that reaches the endometrial</p> <p>16 cavity, fallopian tubes, ovaries and</p> <p>17 peritoneum, may elicit a foreign body type</p> <p>18 reaction and inflammatory response that, in</p> <p>19 some exposed women, may progress to</p> <p>20 epithelial cancers.</p> <p>21 You see that language that I</p> <p>22 just read?</p> <p>23 A. Yes. Again, that's one</p> <p>24 sentence in that paragraph that I believe</p>	<p style="text-align: right;">Page 328</p> <p>1 document.</p> <p>2 When he says in this paragraph,</p> <p>3 in part: Combine this evidence with the</p> <p>4 theory that talc deposition on the ovarian</p> <p>5 epithelium initiates epithelium inflammation.</p> <p>6 Is that in the same genre as</p> <p>7 the same thing, the same mechanism that we've</p> <p>8 talked about in each of these articles where</p> <p>9 there's a foreign body present on tissue and</p> <p>10 the reaction of the tissue is inflammation?</p> <p>11 MR. FROST: Objection.</p> <p>12 A. Well, again, as I said</p> <p>13 previously with the FDA letter, this is the</p> <p>14 personal correspondence. He refers to a</p> <p>15 theory. Without more information about what</p> <p>16 is he referring to, I can't speak to what he</p> <p>17 is -- what is he speaking to.</p> <p>18 BY MR. SOILEAU:</p> <p>19 Q. But that is what you said in</p> <p>20 the article that you helped write, Tuttle</p> <p>21 Exhibit 30, an inflammatory process that you</p> <p>22 describe under Mechanism of Toxicity. You</p> <p>23 know what that means.</p> <p>24 You helped write -- you signed</p>
<p style="text-align: right;">Page 327</p> <p>1 we've revisited -- we visited previously.</p> <p>2 Q. Isn't the foreign body type</p> <p>3 reaction and inflammatory response that is</p> <p>4 noted here in the FDA paper from 2014</p> <p>5 referring to the same sort of foreign body</p> <p>6 type reaction and inflammatory response that</p> <p>7 you discuss in Tuttle Exhibit 30 under</p> <p>8 Mechanism of Toxicity?</p> <p>9 MR. FROST: Objection.</p> <p>10 A. I don't know. As previously</p> <p>11 stated, this is a letter. They don't cite</p> <p>12 references. We're talking about the ovaries</p> <p>13 and other avenues of the female reproductive</p> <p>14 system compared to the lung, which is what we</p> <p>15 were discussing in this synthetic vitreous</p> <p>16 fibers study.</p> <p>17 So as we said before, the</p> <p>18 inflammatory response is diverse and</p> <p>19 complicated, so, no, I don't know.</p> <p>20 BY MR. SOILEAU:</p> <p>21 Q. What about from Exhibit 22,</p> <p>22 which is the cover transmission to Mr. Ashton</p> <p>23 from Zaren- -- Zazenski, I'm sorry,</p> <p>24 Z-A-R-E-N-S-K-I -- a name we saw in another</p>	<p style="text-align: right;">Page 329</p> <p>1 off on Mechanism of Toxicity under article --</p> <p>2 I'm sorry, under Tuttle Exhibit 30.</p> <p>3 MR. FROST: Is there a</p> <p>4 question? Objection.</p> <p>5 BY MR. SOILEAU:</p> <p>6 Q. You're telling me that the FDA</p> <p>7 letter and Exhibit 22 that I've shown you,</p> <p>8 which talk about inflammation, that you</p> <p>9 don't -- you don't seem to know enough about</p> <p>10 them to comment on them. And I was just</p> <p>11 asking, you know enough to comment about</p> <p>12 Exhibit 30, your article, don't you?</p> <p>13 MR. FROST: Objection,</p> <p>14 misstates testimony.</p> <p>15 A. Well, again, as I said, we</p> <p>16 wrote this, you know, several years ago,</p> <p>17 looks like in 2014, and, you know, we're</p> <p>18 speaking very generally about the</p> <p>19 inflammatory process in the lung in this</p> <p>20 particular area.</p> <p>21 As we discussed previously,</p> <p>22 when looking at the defense mechanisms of the</p> <p>23 body, I have not done -- I've not compared</p> <p>24 all the organs of the body and their various</p>



Kelly Tuttle, Ph.D.

<p style="text-align: right;">Page 330</p> <p>1 defense mechanisms, and I think I've said  2 several times that the inflammatory response  3 is very complex and there's a lot of  4 different cells and cytokines and things  5 involved, which we don't discuss in this  6 Mechanisms of Toxicity. It's a very general  7 paragraph that we're discussing.  8 And I have not, I think I said  9 earlier, brushed up on my understanding of  10 the mechanistic toxicology or the mechanisms  11 revolving inflammation in regards to my  12 report or the assessment of talcum powder and  13 ovarian cancer.  14 BY MR. SOILEAU:  15 Q. Well, given that, Doctor, isn't  16 it is it fair to say that you cannot offer  17 opinions on the existence or nonexistence of  18 a plausible mechanism for ovarian cancer that  19 involves foreign particles, inflammation and  20 a cascade of events that results in  21 carcinogenicity?  22 MR. FROST: Objection.  23 BY MR. SOILEAU:  24 Q. Well, you're not in a position</p>	<p style="text-align: right;">Page 332</p> <p>1 looked at the defense mechanisms of the  2 ovary, correct?  3 MR. FROST: Objection.  4 A. I said I've not done research  5 into the defense mechanisms of the ovary or  6 any, you know, specifics in regards to the  7 defense mechanisms of the ovary.  8 BY MR. SOILEAU:  9 Q. You looked at migration, right?  10 A. I looked at the scientific  11 evidence of whether there was any support for  12 the theory of external migration from  13 perineal application of talc to the ovaries.  14 Q. And you found no evidence?  15 A. That's correct, the scientific  16 evidence does not support the migration  17 theory.  18 Q. You did not look at evidence  19 involving the existence of talc within  20 ovarian tissue, did you?  21 MR. FROST: Objection.  22 A. As I think we discussed  23 previously in the -- as far as the presence  24 of talc in ovarian tissue, we -- in regards</p>
<p style="text-align: right;">Page 331</p> <p>1 to comment on that today?  2 MR. FROST: Objection.  3 A. There were --  4 THE WITNESS: I'm sorry.  5 A. There were multiple parts to  6 that question. Can we break it --  7 BY MR. SOILEAU:  8 Q. Right. But they all go back to  9 what we're talking about.  10 Isn't it fair to say, Doctor,  11 that you're not in a position today, you do  12 not have a foundation from which to offer an  13 opinion on the existence or nonexistence of a  14 plausible mechanism for talc particles to  15 trigger ovarian cancer?  16 MR. FROST: Objection.  17 A. So that's a -- that's a  18 different question than what you were asking  19 previously.  20 BY MR. SOILEAU:  21 Q. It is, but you've told me  22 today -- let's back up for a step or two and  23 I'll lay it out better.  24 You've told me you've not</p>	<p style="text-align: right;">Page 333</p> <p>1 to the migration theory, I looked at  2 scientific evidence on whether there was any  3 evidence to support the theory that external  4 application of talc would migrate to the  5 ovaries.  6 BY MR. SOILEAU:  7 Q. Do you have an opinion, Doctor,  8 as to whether there is evidence to support a  9 potential mechanism for talc to cause ovarian  10 cancer following perineal application?  11 MR. FROST: Objection.  12 A. As I state in my report when  13 looking at the biological plausibility in the  14 Hill criteria, I base my scientific evidence  15 of the migration theory that the talc will  16 reach the ovaries based on perineal  17 application for which the scientific evidence  18 doesn't support that.  19 BY MR. SOILEAU:  20 Q. Here's what I hear you telling  21 me, and you've been over it a few times, many  22 times today, and that is, you do not see  23 scientific evidence to support the ability of  24 talcum powder applied to the perineum to</p>

<p style="text-align: right;">Page 334</p> <p>1 migrate to the ovaries. Therefore, you've</p> <p>2 not looked at any mechanistic issues</p> <p>3 involving talc reaching the ovaries because</p> <p>4 you don't believe it happens.</p> <p>5 MR. FROST: Objection.</p> <p>6 BY MR. SOILEAU:</p> <p>7 Q. And I'm just trying to figure</p> <p>8 out if you have an opinion, one way or</p> <p>9 another, about any potential mechanism. And</p> <p>10 from what you've told me, it wouldn't seem</p> <p>11 like you had developed a foundation from</p> <p>12 which to speak to that.</p> <p>13 MR. FROST: Objection.</p> <p>14 A. Well, as I said, I didn't do an</p> <p>15 extensive review regarding the genetic</p> <p>16 mechanisms of inflammation, and again,</p> <p>17 inflammation is not the same as the</p> <p>18 initiation of cancer.</p> <p>19 And so, you know, I did not do</p> <p>20 a detailed review regarding the inflammatory</p> <p>21 process. We talked -- we quoted a few</p> <p>22 sentences from the paragraph that I have on</p> <p>23 page 27 where I look briefly at some of the</p> <p>24 studies that look at talc inflammation and</p>	<p style="text-align: right;">Page 336</p> <p>1 BY MR. SOILEAU:</p> <p>2 Q. Do you know?</p> <p>3 A. Again, I --</p> <p>4 MR. FROST: Objection.</p> <p>5 A. I am aware generally that there</p> <p>6 are a very few number of cancers for which</p> <p>7 initiation [sic] may be involved in the</p> <p>8 initiation process. I think that there's</p> <p>9 somebody else, another expert, that discusses</p> <p>10 that specifically.</p> <p>11 In my report when I discussed</p> <p>12 carcinogenesis, inflammation is more</p> <p>13 associated with promotion rather than</p> <p>14 initiation.</p> <p>15 BY MR. SOILEAU:</p> <p>16 Q. Today is my opportunity to talk</p> <p>17 to you. Should I expect that you would come</p> <p>18 into the courtroom and offer an opinion for</p> <p>19 or against the existence of a plausible</p> <p>20 mechanism for the development of ovarian</p> <p>21 cancer triggered by talc on the ovaries?</p> <p>22 MR. FROST: Objection.</p> <p>23 Objection.</p> <p>24 A. I'm sorry, can you...</p>
<p style="text-align: right;">Page 335</p> <p>1 ovarian cancer, but I have not done a</p> <p>2 detailed assessment of the inflammatory</p> <p>3 process or the genetic mechanism; therefore,</p> <p>4 I think there are others that do that.</p> <p>5 BY MR. SOILEAU:</p> <p>6 Q. It can be though, right?</p> <p>7 MR. FROST: Objection.</p> <p>8 A. I'm sorry?</p> <p>9 BY MR. SOILEAU:</p> <p>10 Q. It can be. Inflammation can be</p> <p>11 a step in the development of cancer?</p> <p>12 MR. FROST: Objection.</p> <p>13 BY MR. SOILEAU:</p> <p>14 Q. Isn't that true?</p> <p>15 MR. FROST: Objection.</p> <p>16 A. I would need more information</p> <p>17 because I think you're referring to promotion</p> <p>18 as opposed to initiation.</p> <p>19 BY MR. SOILEAU:</p> <p>20 Q. I was just asking if</p> <p>21 inflammation can be an initial step in the</p> <p>22 body that ultimately develops into a cancer.</p> <p>23 MR. FROST: Objection.</p> <p>24 ///</p>	<p style="text-align: right;">Page 337</p> <p>1 BY MR. SOILEAU:</p> <p>2 Q. I'm just trying to figure out</p> <p>3 if you have an opinion one way or another on</p> <p>4 the question of: Is there a plausible</p> <p>5 mechanism for talc to produce or contribute</p> <p>6 as a significant factor to the development of</p> <p>7 ovarian cancer?</p> <p>8 MR. FROST: Objection.</p> <p>9 A. So again, you know, my opinions</p> <p>10 in my report are stated, and I briefly touch</p> <p>11 upon inflammation. That being said, my --</p> <p>12 the scientific evidence does not support a</p> <p>13 causal association between talc and ovarian</p> <p>14 cancer. In regards to a plausible mechanism,</p> <p>15 we already discussed migration in depth. I</p> <p>16 don't, I believe, get into migration or, as I</p> <p>17 said, the mechanistics of inflammation in</p> <p>18 great detail in my report.</p> <p>19 I look at the scientific</p> <p>20 literature very generally. There are others</p> <p>21 that get more in depth as far as mechanisms</p> <p>22 than I do.</p> <p>23 BY MR. SOILEAU:</p> <p>24 Q. Well, you've just got that one</p>

Kelly Tuttle, Ph.D.

<p style="text-align: right;">Page 338</p> <p>1 paragraph on inflammation, right?</p> <p>2 MR. FROST: Objection.</p> <p>3 A. I would need to go through. As</p> <p>4 I said, I think in the carcinogenesis portion</p> <p>5 of my report, I discuss inflammation briefly</p> <p>6 as well in a general role --</p> <p>7 BY MR. SOILEAU:</p> <p>8 Q. Right.</p> <p>9 A. -- regarding carcinogenicity.</p> <p>10 Q. That's true. Right. And</p> <p>11 that's fair.</p> <p>12 I meant in the context of talc,</p> <p>13 you only have this one paragraph at page 27,</p> <p>14 7.3.3.</p> <p>15 A. I -- as I said, I don't get</p> <p>16 into the mechanisms of inflammation in great</p> <p>17 detail. I do believe that in discussing</p> <p>18 fragrant chemicals, there's also some</p> <p>19 references to irritation and potentially</p> <p>20 inflammation, but without doing a quick word</p> <p>21 search on it, I can't speak that this is the</p> <p>22 only place that I mention inflammation other</p> <p>23 than what we discussed in the --</p> <p>24 Q. Okay. Just to be clear, I</p>	<p style="text-align: right;">Page 340</p> <p>1 MR. FROST: Objection.</p> <p>2 A. As I said, I have experience</p> <p>3 and expertise in inflammation and researching</p> <p>4 inflammation. As I said previously, I did</p> <p>5 not research -- brush up on the mechanisms of</p> <p>6 the -- the inflammatory process and the</p> <p>7 mechanisms, I don't get into that, into my --</p> <p>8 in my report in this case.</p> <p>9 BY MR. SOILEAU:</p> <p>10 Q. Is talc cytotoxic?</p> <p>11 A. I don't know.</p> <p>12 Q. Okay. Let me show you an</p> <p>13 exhibit I will mark as Tuttle Exhibit 31.</p> <p>14 (Whereupon, Deposition Exhibit</p> <p>15 Tuttle-31, 2/17/77 Schneider Letter,</p> <p>16 was marked for identification.)</p> <p>17 MR. SOILEAU: The only copies</p> <p>18 we have, for the record, have some</p> <p>19 highlighting on them, and we've not</p> <p>20 been able to get that off. So every</p> <p>21 copy will have the same highlighting.</p> <p>22 It's not highlighting that I applied.</p> <p>23 And I really suspect you guys know</p> <p>24 that already. What that's?</p>
<p style="text-align: right;">Page 339</p> <p>1 didn't really -- I really meant specifically</p> <p>2 inflammation and talc. I know that</p> <p>3 inflammation is discussed elsewhere when you</p> <p>4 talk about carcinogenicity.</p> <p>5 What is cytotoxicity?</p> <p>6 A. Goodness. That is --</p> <p>7 Q. Did I step out of your area?</p> <p>8 MR. FROST: Objection.</p> <p>9 A. I'm not comfortable answering</p> <p>10 it off the cuff. I'm not sure that I can</p> <p>11 define it very clearly and scientifically.</p> <p>12 BY MR. SOILEAU:</p> <p>13 Q. What relevance, if any, does</p> <p>14 cytotoxicity have for discussion like the one</p> <p>15 we're having today?</p> <p>16 MR. FROST: Objection.</p> <p>17 A. Again, we're getting a little</p> <p>18 out of what I did in regards to my report and</p> <p>19 what I researched for --</p> <p>20 BY MR. SOILEAU:</p> <p>21 Q. Okay. All right.</p> <p>22 A. -- the scientific literature.</p> <p>23 Q. Are we getting out of your area</p> <p>24 of expertise?</p>	<p style="text-align: right;">Page 341</p> <p>1 MR. FROST: I believe I've seen</p> <p>2 this highlighting before.</p> <p>3 MR. SOILEAU: Yes. I thought</p> <p>4 as much.</p> <p>5 MR. FROST: Is this 31?</p> <p>6 THE WITNESS: Yes.</p> <p>7 MR. FROST: I believe this was</p> <p>8 highlighted once for trial.</p> <p>9 MR. SOILEAU: I think everyone</p> <p>10 in the room knows more about these</p> <p>11 exhibits than I do, so I appreciate</p> <p>12 that. Trying to keep up.</p> <p>13 BY MR. SOILEAU:</p> <p>14 Q. Do you see the name Battelle at</p> <p>15 the top?</p> <p>16 A. Yes, I do.</p> <p>17 Q. The third page of this</p> <p>18 three-page document, it's signed by</p> <p>19 R.P. Schneider, Ph.D., assistant manager,</p> <p>20 molecular biology and biophysics.</p> <p>21 Do you recognize that name?</p> <p>22 A. Not off the top of my head, no.</p> <p>23 Q. It begins saying -- what about</p> <p>24 William Sherman? I'm sorry, William Sherman,</p>

86 (Pages 338 to 341)

Kelly Tuttle, Ph.D.

<p style="text-align: right;">Page 342</p> <p>1 Ph.D., manager of biomedical evaluations, 2 Johnson &amp; Johnson Baby Products Company. 3 Do you know who that is? 4 A. No, I don't. 5 Q. Okay. And this goes all the 6 way back to February 17, 1977. 7 It says: Dear Bill, as I 8 related to you on the telephone, we have 9 spent more time studying the effects of talc 10 than we anticipated. Since we have found a 11 cytotoxic effect, I felt that we should 12 pursue it in more detail and obtain data 13 which can be compared to other studies. This 14 has required doing more short-term incubation 15 experiments in the absence of serum. 16 Is a cytotoxic effect for talc 17 significant to you as a toxicologist? 18 MR. FROST: Objection. 19 A. It depends. I would need more 20 information. I would need to see the studies 21 that they're discussing. You know, this is, 22 again, a personal communication. This isn't 23 a research article where they're discussing 24 the studies that they're performing.</p>	<p style="text-align: right;">Page 344</p> <p>1 organisms, including the environment. 2 Q. And at a most basic level, 3 doesn't cytotoxic mean that it is toxic -- 4 the agent or substance is toxic to the cells 5 of the body? 6 MR. FROST: Objection. 7 A. Again, as I said earlier, I'm 8 not sure that I can accurately define 9 cytotoxicity just off the cuff without 10 referring to a document. 11 BY MR. SOILEAU: 12 Q. Okay. 13 A. I don't want to use layman 14 terms and then be inaccurate or misspeak. 15 Q. I can show it to you if we need 16 to, but the Wehner document, one of the 17 Wehner documents we looked at earlier, talked 18 about intended or normal use of talcum powder 19 products. 20 Have you seen that phrase in 21 your work on this project, intended or normal 22 use of talcum powder products? 23 A. I didn't specifically look for 24 that phrase in my assessment of the</p>
<p style="text-align: right;">Page 343</p> <p>1 BY MR. SOILEAU: 2 Q. Okay. But I'm simply asking 3 you a general question right now, Dr. Tuttle. 4 If talc is cytotoxic, is that 5 relevant to your opinions in this case? 6 MR. FROST: Objection. 7 A. Again, you know, my opinions 8 are -- you know, cytotoxic, again, it would 9 depend on these studies and what information 10 is being shown. But as I said previously, I 11 assessed the scientific literature regarding 12 the -- whether the exposure to talcum powder 13 perineally, what -- the scientific evidence 14 showed a causal association between perineal 15 talcum powder exposure and ovarian cancer. 16 BY MR. SOILEAU: 17 Q. We said at the beginning of our 18 discussion today, and I think we agreed that 19 toxicology includes the study of adverse 20 effects of agents on organisms, right? 21 A. Generally speaking, yes, the 22 science of toxicology is the study of 23 potential adverse health effects relating to 24 dose and exposure metrics on living</p>	<p style="text-align: right;">Page 345</p> <p>1 scientific literature, so I couldn't say. 2 Q. Do you have an understanding 3 whether genital application of talcum powder 4 products is considered a normal and intended 5 use of the product? 6 MR. FROST: Objection. 7 BY MR. SOILEAU: 8 Q. I'm just asking if you have an 9 understanding. 10 MR. FROST: Objection. 11 A. I'm -- I don't know. As I 12 said, I didn't look for that phrase in my 13 assessment of the scientific literature. I 14 merely looked at whether the scientific 15 evidence for the perineal use of talcum 16 powder, if the scientific evidence supported 17 a causal association with ovarian cancer. 18 BY MR. SOILEAU: 19 Q. But you did not consider the 20 possibility that talc was cytotoxic, correct? 21 MR. FROST: Objection. 22 A. Well, again, in looking at 23 whether there is a causal association when 24 you're looking at the epidemiological studies</p>

Kelly Tuttle, Ph.D.

<p style="text-align: right;">Page 346</p> <p>1 or, you know, the study cited in the report,  2 you know, looking for that causal  3 association, as I said before, I didn't get  4 into the genetic mechanisms as far as we  5 discussed with inflammation or cytotoxicity,  6 but looking at the body of evidence to see  7 whether there is a causal association.  8 BY MR. SOILEAU:  9 Q. Back on the Health Canada study  10 for just a moment. I think we discussed that  11 you had cited it in your report, of course,  12 the draft assessment?  13 A. Yes. Can you refer me to which  14 exhibit number it is?  15 Q. I can. My question is more  16 general, but I'm glad to tell you which  17 exhibit number it is.  18 I'm going to tell you my  19 question is: Are you familiar with the  20 methodology that Health Canada uses?  21 I think you'll find that it's  22 Exhibit 21.  23 A. Thank you.  24 And can you repeat your</p>	<p style="text-align: right;">Page 348</p> <p>1 Tuttle-32, Health Canada Risk  2 Assessment Framework Study, was marked  3 for identification.)  4 BY MR. SOILEAU:  5 Q. Have you seen this before? It  6 says Risk Assessment Framework Summary, and  7 it's -- well, it speaks for itself.  8 Have you seen that before or do  9 you know?  10 A. No, I don't believe I have.  11 Q. I'm really just asking whether,  12 as we sit here today, having had the  13 opportunity to look at the Health Canada  14 draft assessment, if you have any criticisms  15 of their methodology or the manner in which  16 they applied their methodology to the  17 evidence that they looked at?  18 MR. FROST: Objection.  19 A. Well, as I said, I -- the  20 methodology -- I haven't reviewed the  21 Exhibit 32 that you provided to me before. I  22 haven't seen it, so I can't discuss the  23 methodology that Health Canada used without  24 some time to look at the methodology.</p>
<p style="text-align: right;">Page 347</p> <p>1 question for me, please?  2 Q. Sure. Are you familiar with  3 the methodology that Health Canada used in  4 preparing the draft assessment?  5 A. I am not specifically familiar  6 with the methodology. As I look at the  7 assessment, I would need to refamiliarize --  8 I think that they go through their  9 methodology in other documents on their  10 website.  11 Q. I think so. I think you're  12 correct.  13 As we sit here today, do you  14 have any criticism of the methodology used by  15 Health Canada in its draft assessment?  16 MR. FROST: Objection.  17 A. Well, as I said before, without  18 having the other documents where they discuss  19 their methodology in detail, I can't discuss  20 it.  21 BY MR. SOILEAU:  22 Q. Let me show you a document I've  23 marked as Exhibit 32, Tuttle Exhibit 32.  24 (Whereupon, Deposition Exhibit</p>	<p style="text-align: right;">Page 349</p> <p>1 BY MR. SOILEAU:  2 Q. You had not considered the  3 actual methodology used by Health Canada when  4 you considered their draft assessment on  5 talc?  6 MR. FROST: Objection.  7 A. As I said, in their draft  8 assessment, they don't really go into their  9 methodology. As I said, I think it was  10 present elsewhere on their framework, but  11 I --  12 BY MR. SOILEAU:  13 Q. My question -- I'm sorry, go  14 ahead.  15 A. No, but I did not review their  16 methodology for their draft screening  17 assessment.  18 Q. Right. That really was my  19 question, that in connection with your review  20 of that document, you did not determine the  21 methodology.  22 MR. FROST: Objection.  23 A. I -- again, I didn't review the  24 methodology that they used.</p>



Kelly Tuttle, Ph.D.

Page 350	Page 352
<p>1 BY MR. SOILEAU:</p> <p>2 Q. Okay. So you would not have</p> <p>3 any criticisms of it, obviously, because it's</p> <p>4 not something you've looked at, fair?</p> <p>5 MR. FROST: Objection.</p> <p>6 A. Again, I would need to look at</p> <p>7 it to be able to discuss it.</p> <p>8 BY MR. SOILEAU:</p> <p>9 Q. Okay. You say in your</p> <p>10 report -- turning to your report, at page 34.</p> <p>11 Let me let you find that. I'm looking at the</p> <p>12 fourth paragraph, the second sentence right</p> <p>13 after footnote 4: This by definition renders</p> <p>14 the products tested as</p> <p>15 nonasbestos-containing.</p> <p>16 You see that?</p> <p>17 A. Yes, I see that.</p> <p>18 Q. And then you cite a document,</p> <p>19 United Nations, 2017?</p> <p>20 A. Yes.</p> <p>21 Q. All right. Let me show you a</p> <p>22 document that I have here.</p> <p>23 THE WITNESS: If I may, while</p> <p>24 he's doing that, how long have we been</p>	<p>1 say: This by definition renders the product</p> <p>2 tested as nonasbestos-containing?</p> <p>3 A. It is one of the references</p> <p>4 that I cite in that paragraph regarding</p> <p>5 asbestos-containing, yes.</p> <p>6 Q. Well, it is the -- let's be</p> <p>7 more specific.</p> <p>8 The sentence that I read: This</p> <p>9 by definition renders the products tested as</p> <p>10 nonasbestos-containing (United Nations,</p> <p>11 2017).</p> <p>12 So there's one citation and</p> <p>13 only one citation, and it is part of that</p> <p>14 sentence, that is, the parenthetical is</p> <p>15 inserted before the period, agreed?</p> <p>16 A. For that specific sentence,</p> <p>17 yes.</p> <p>18 Q. Okay. And so my question to</p> <p>19 you is whether Tuttle Exhibit 33 that I have</p> <p>20 marked and presented to you here today is, in</p> <p>21 fact, the United Nations 2017 document that</p> <p>22 you reference in that sentence on page 34 of</p> <p>23 your report?</p> <p>24 A. Well, the cover page says that</p>
Page 351	Page 353
<p>1 going?</p> <p>2 THE VIDEOGRAPHER: One hour and</p> <p>3 10 minutes.</p> <p>4 MR. SOILEAU: I only have two</p> <p>5 copies of this. I'm going to give one</p> <p>6 to the witness and one to counsel to</p> <p>7 sort of share.</p> <p>8 MR. FROST: Sure.</p> <p>9 MR. SOILEAU: Let me go ahead</p> <p>10 and put a number on it. This will be</p> <p>11 identified as Tuttle Exhibit 33.</p> <p>12 (Whereupon, Deposition Exhibit</p> <p>13 Tuttle-33, Global Harmonized System of</p> <p>14 Classification and Labeling of</p> <p>15 Chemicals, was marked for</p> <p>16 identification.)</p> <p>17 MR. SOILEAU: I could not find</p> <p>18 a way to make this smaller under the</p> <p>19 circumstances.</p> <p>20 BY MR. SOILEAU:</p> <p>21 Q. My question, Doctor, my first</p> <p>22 question applicable to this exhibit, Tuttle</p> <p>23 Exhibit 33: Is this the exhibit that you</p> <p>24 reference at page 34 of your report when you</p>	<p>1 it is. It is a large and sizable document,</p> <p>2 so I don't know if it's here in its entirety.</p> <p>3 But the cover page says it is the Globally</p> <p>4 Harmonized System of Classification and</p> <p>5 Labeling of Chemicals.</p> <p>6 Q. All right, Doctor. Are you</p> <p>7 familiar with that document?</p> <p>8 A. Yes.</p> <p>9 Q. For example, have you used it</p> <p>10 before?</p> <p>11 A. Yes, I've used this document.</p> <p>12 Q. Do you maintain, Doctor, that</p> <p>13 this exhibit, Tuttle Exhibit 33, the United</p> <p>14 Nations document, includes a definition of</p> <p>15 the term "nonasbestos-containing"?</p> <p>16 A. No, I don't believe it provides</p> <p>17 a verbatim definition of</p> <p>18 nonasbestos-containing.</p> <p>19 Q. Do you know if the term</p> <p>20 "asbestos" or the words "asbestos-containing"</p> <p>21 appear anywhere in the document?</p> <p>22 A. No. I -- I don't know</p> <p>23 specifically. I would have to do a check if</p> <p>24 they reference asbestos-containing in the</p>

Kelly Tuttle, Ph.D.

<p style="text-align: right;">Page 354</p> <p>1 document, but in regards to, you know, the 2 classification and labeling as far as the 3 information provided, I don't believe so. 4 Q. I can only tell you that I did 5 and I couldn't find those words, and I'm not 6 going to ask you to do it right now. 7 But why do you reference a 8 definition citing this paper if there is no 9 actual definition of nonasbestos-containing, 10 that terminology, in this document? 11 MR. FROST: Objection. 12 A. So again, this is one of the 13 references I cite, and the reason I cite it 14 is when you go through the Global 15 Harmonization Standard, it is a standard 16 that, as it states on the label, provides the 17 guidelines that the United Nations and OSHA, 18 the Occupational Safety and Health 19 Administration, have put forth regarding 20 classification and labeling of chemicals. 21 And the reason that that is 22 important -- and I think I discuss it in more 23 detail in other parts of my report -- 24 actually, I do at the bottom of that same</p>	<p style="text-align: right;">Page 356</p> <p>1 Q. I appreciate that. I'm 2 really -- I was asking you whether, as a 3 carcinogen, asbestos included -- or it was 4 determined that asbestos caused, among the 5 cancers it causes, ovarian cancer? 6 MR. FROST: Objection. 7 MR. SOILEAU: Yeah, that's not 8 really a question, so it's okay. 9 BY MR. SOILEAU: 10 Q. I'm still a little lost -- I 11 guess we can just agree on this: That 12 document, Tuttle Exhibit 33, does not include 13 a specific definition of 14 nonasbestos-containing, agreed? 15 MR. FROST: Objection. 16 A. Again, as I said, this provides 17 guidelines regarding whether components need 18 to be listed as an ingredient on an MSDS or 19 need to be listed or taken into account when 20 assessing labeling or hazard assessment 21 guidelines and things like that for which 22 they have a .1% cutoff for carcinogens such 23 as asbestos. 24 ///</p>
<p style="text-align: right;">Page 355</p> <p>1 page, they provide information regarding 2 substances and concentration limits in 3 regards to hazard labels, hazard 4 identifications, and for -- in this 5 particular case we're referring to asbestos, 6 and they provide for carcinogens a .1% cutoff 7 in regards to labeling or including a 8 material as being present in a compound on an 9 MSDS or on a hazard label or identification 10 label. 11 BY MR. SOILEAU: 12 Q. Is asbestos a carcinogen? 13 A. IARC has classified asbestos as 14 a known human carcinogen. 15 Q. Is asbestos a known carcinogen 16 for ovarian cancer? 17 A. I believe I discussed this in 18 my report. I believe IARC found that the 19 heavy occupational levels of asbestos 20 exposure associated with ovarian cancer, I 21 can't remember offhand if they also 22 classified it as a Group 1, but they 23 certainly said that heavy occupational 24 exposures are associated with ovarian cancer.</p>	<p style="text-align: right;">Page 357</p> <p>1 BY MR. SOILEAU: 2 Q. There's no definition of 3 nonasbestos-containing in Tuttle Exhibit 33, 4 is there, Doctor? 5 MR. FROST: Objection. 6 A. Again, as I said, it provides 7 guidelines on whether something is required 8 to be included on an MSDS as an ingredient or 9 a component of a product, and guidelines 10 regarding the labeling and hazard 11 identification. 12 BY MR. SOILEAU: 13 Q. Is it your testimony to this 14 court, Doctor, that as you suggest on page 34 15 of your report, Tuttle Exhibit 33 includes a 16 definition of nonasbestos-containing? 17 MR. FROST: Objection, 18 misstates the report, misstates her 19 testimony. 20 A. Again, so as I state in that 21 one sentence and later on again I cite 22 something, the EPA guidelines, which do offer 23 a specific definition for 24 asbestos-containing, which is actually more</p>

90 (Pages 354 to 357)

Kelly Tuttle, Ph.D.

Page 358	Page 360
<p>1 lenient than the Global Harmonization</p> <p>2 Standard.</p> <p>3 What the Global Harmonization</p> <p>4 Standard does is provide guidelines over what</p> <p>5 is required to be listed as an ingredient or</p> <p>6 component in regards to labeling.</p> <p>7 MR. SOILEAU: I think I'm just</p> <p>8 required to move to strike as</p> <p>9 nonresponsive.</p> <p>10 BY MR. SOILEAU:</p> <p>11 Q. You didn't cite EPA in that</p> <p>12 sentence, did you?</p> <p>13 MR. FROST: Objection.</p> <p>14 A. No, I cite it in the next</p> <p>15 sentence, I believe.</p> <p>16 BY MR. SOILEAU:</p> <p>17 Q. Well, you cite many, many</p> <p>18 articles through your report. I mean, you've</p> <p>19 got pages and pages of references that you</p> <p>20 cite through your report, right?</p> <p>21 A. Yes, that's true.</p> <p>22 Q. But I'm only asking about one</p> <p>23 sentence. You understand that?</p> <p>24 A. Well, again, you're asking</p>	<p>1 Standard does, as I said previously, provides</p> <p>2 guidelines on whether materials have to be</p> <p>3 included as an ingredient in a material</p> <p>4 safety data sheet or on a label or a hazard</p> <p>5 label put on a product.</p> <p>6 Q. Is that the best answer you can</p> <p>7 offer to the question I asked?</p> <p>8 MR. FROST: Objection.</p> <p>9 A. I'm trying to be as clear as I</p> <p>10 can be.</p> <p>11 BY MR. SOILEAU:</p> <p>12 Q. I have to disagree with you,</p> <p>13 Doctor. I'm asking you if the document in</p> <p>14 front of you includes a definition of</p> <p>15 nonasbestos-containing, and it can be no, yes</p> <p>16 or I don't know.</p> <p>17 MR. FROST: Objection, asked</p> <p>18 and answered.</p> <p>19 BY MR. SOILEAU:</p> <p>20 Q. But it is the one document --</p> <p>21 MR. SOILEAU: It has been</p> <p>22 asked, but it has not been answered.</p> <p>23 MR. FROST: Disagree.</p> <p>24 Objection.</p>
Page 359	Page 361
<p>1 about an asbestos-containing definition, and</p> <p>2 in the very next sentence in my report --</p> <p>3 Q. No. No, I'm asking you: You</p> <p>4 say this by definition -- and you used the</p> <p>5 words "nonasbestos-containing." You open</p> <p>6 paren, United Nations, comma, 2017, close</p> <p>7 paren, period. It is the only citation you</p> <p>8 offer for that sentence.</p> <p>9 And I'm asking you if you can</p> <p>10 at least acknowledge for the record that that</p> <p>11 document, in its many, many pages, Tuttle</p> <p>12 Exhibit 33 does not include a definition of</p> <p>13 nonasbestos-containing.</p> <p>14 MR. FROST: Objection.</p> <p>15 BY MR. SOILEAU:</p> <p>16 Q. That's all I'm asking. It's</p> <p>17 very straightforward.</p> <p>18 A. Well, again, the reason it is</p> <p>19 the only reference cited in that particular</p> <p>20 point is we are talking about the .1% cutoff.</p> <p>21 In the next sentence we go to the 1% cutoff</p> <p>22 established by US EPA that does actually</p> <p>23 define asbestos-containing.</p> <p>24 What the Global Harmonization</p>	<p>1 MR. SOILEAU: Well, you're</p> <p>2 stipulating that it's not in there?</p> <p>3 MR. FROST: I'm not testifying</p> <p>4 here today.</p> <p>5 MR. SOILEAU: Do you stipulate</p> <p>6 that she has testified it's not in</p> <p>7 there?</p> <p>8 MR. FROST: I -- the record</p> <p>9 says what it says.</p> <p>10 MR. SOILEAU: Very good. I</p> <p>11 agree.</p> <p>12 MR. FROST: I stipulate that</p> <p>13 you've asked this question several</p> <p>14 times and the witness has given</p> <p>15 answers to it several times.</p> <p>16 MR. SOILEAU: I will agree with</p> <p>17 that.</p> <p>18 BY MR. SOILEAU:</p> <p>19 Q. It's not in there, is it,</p> <p>20 Doctor?</p> <p>21 MR. FROST: Objection.</p> <p>22 A. So --</p> <p>23 BY MR. SOILEAU:</p> <p>24 Q. You can't say it?</p>

Kelly Tuttle, Ph.D.

<p style="text-align: right;">Page 362</p> <p>1 A. Again, as I said before, I 2 don't believe the word "asbestos-containing" 3 specifically occurs in this document, but 4 that being said, there are guidelines 5 regarding whether the -- and again, it's 6 that .1%, whether a material is required 7 under the Global Harmonization Standard to be 8 listed as an ingredient of a product on a 9 material safety data sheet or on a label. 10 Q. Let's look at what I have 11 marked as Tuttle Exhibit 34. 12 (Whereupon, Deposition Exhibit 13 Tuttle-34, IARC Monograph on Asbestos, 14 was marked for identification.) 15 THE WITNESS: If I may, I'm 16 going to need a short break in the 17 near future. 18 MR. SOILEAU: We're going to 19 take it as soon as we look at this. I 20 was thinking the same. 21 THE WITNESS: Okay. 22 BY MR. SOILEAU: 23 Q. Do you recognize the document 24 that I have given you as Tuttle Exhibit 34?</p>	<p style="text-align: right;">Page 364</p> <p>1 and I don't see what I want to ask you 2 about, and I don't want you to sit 3 here while I look for it. 4 So we'll take our break now and 5 come back and I'll pick up with this 6 document. 7 THE VIDEOGRAPHER: Going off 8 the record at 4:56 p.m. 9 (Recess taken, 4:56 p.m. to 10 5:06 p.m.) 11 THE VIDEOGRAPHER: We're back 12 on the record at 5:06 p.m. 13 BY MR. SOILEAU: 14 Q. Okay. Doctor, I think we've 15 reached our last session for this deposition. 16 Are you ready to proceed? 17 A. Yes, I am. 18 Q. What is fibrous talc? 19 A. So I'm going to be speaking, 20 you know, without exact definitions in front 21 of me, but it is my general understanding 22 that fibrous talc is an elongated particle 23 that meets the World Health Organization or 24 OSHA definitions in regarding to fiber size.</p>
<p style="text-align: right;">Page 363</p> <p>1 A. Yes, I do. 2 Q. What is it? 3 A. I believe it is the IARC 4 monograph for asbestos. 5 Q. All right. 6 MR. FROST: Again, I just want 7 to -- for the record, this is the 8 2012, the 100C? It doesn't have a 9 cover on it. 10 MR. SOILEAU: I believe that 11 this is 100C, and I'm sorry, I don't 12 see it. 13 MR. FROST: That's okay. I 14 just wanted to make the record clear 15 because there are two asbestos 16 monographs. 17 MR. SOILEAU: I agree. 18 THE WITNESS: That's true. 19 Thank you. 20 MR. FROST: Well, that's true. 21 There are some older ones. 22 MR. SOILEAU: I think what 23 we'll do is go ahead and take a break 24 because I have a page reference here</p>	<p style="text-align: right;">Page 365</p> <p>1 Q. Is the question of fibrous talc 2 relevant to the issues that we discussed here 3 today? 4 MR. FROST: Objection, vague. 5 A. Generally speaking, you know, 6 in regards to assessing the causal 7 association between talcum powder and ovarian 8 cancer, the testing that we look at in the 9 scientific literature regarding talcum powder 10 insofar as it contains any materials, you 11 know, that would be included in those -- 12 those studies. 13 BY MR. SOILEAU: 14 Q. Do the talcum powder products 15 sold by Johnson &amp; Johnson include, in part, 16 fibrous talc? 17 MR. FROST: Objection, outside 18 of this witness' area of expertise. 19 BY MR. SOILEAU: 20 Q. Is that true? 21 A. Again, I do not -- I think I 22 have one section where I discuss fibrous talc 23 and it's not in relation to its content or 24 lack thereof in Johnson &amp; Johnson baby powder</p>

92 (Pages 362 to 365)

Kelly Tuttle, Ph.D.

Page 366	Page 368
<p>1 products.</p> <p>2 As we discussed earlier, I'm</p> <p>3 not a mineralogist. I'm not a geologist. I</p> <p>4 do not offer any opinions in regards to that.</p> <p>5 I believe others get into the mineralogy more</p> <p>6 than I do.</p> <p>7 Q. Do you know whether fibrous</p> <p>8 talc is carcinogenic?</p> <p>9 A. I am not aware that fibrous</p> <p>10 talc has been classified as a carcinogen.</p> <p>11 Q. All right. Did you rely on any</p> <p>12 of the testing documents that are part of</p> <p>13 Appendix C, and specifically the asbestos</p> <p>14 test in those documents?</p> <p>15 A. Again, in my report, I do not</p> <p>16 get into specifically the testing. I don't</p> <p>17 reference the asbestos testing in those</p> <p>18 documents in my report. I look at the</p> <p>19 scientific literature. I do believe I</p> <p>20 reference the FDA testing of Johnson &amp;</p> <p>21 Johnson baby powder regarding asbestos.</p> <p>22 In my report, I look at</p> <p>23 Drs. Longo and Rigler, but I don't believe I</p> <p>24 look at those Imerys and J&amp;J documents as far</p>	<p>1 testing in the appendix, and -- but I did not</p> <p>2 summarize it in my report. I don't recall.</p> <p>3 If they looked at the baby powder</p> <p>4 specifically. I know that there was asbestos</p> <p>5 testing done and I think that they did have</p> <p>6 some detections.</p> <p>7 But again, I did not assess the</p> <p>8 methodology or the results to be able to</p> <p>9 discuss those. As I understand, there are</p> <p>10 others who have done that in more detail,</p> <p>11 and, you know, they have more -- as I said,</p> <p>12 I'm not a mineralogist and they discuss that</p> <p>13 in more detail as regards to the methodology.</p> <p>14 Q. So are there any positive</p> <p>15 findings, though, included in those many</p> <p>16 pages of charts?</p> <p>17 MR. FROST: Objection.</p> <p>18 A. Again, we can go through each</p> <p>19 individual chart. I am not aware</p> <p>20 specifically of any specific to Johnson &amp;</p> <p>21 Johnson baby powder. As I said, I know</p> <p>22 there's asbestos testing throughout the</p> <p>23 table, some of which were positive, but I did</p> <p>24 not assess them or look at the methodology</p>
Page 367	Page 369
<p>1 as assessing asbestos content in the</p> <p>2 Johnson &amp; Johnson's baby powder.</p> <p>3 Q. Do you know whether any of the</p> <p>4 tests were positive for asbestos, that is,</p> <p>5 the test results included in Appendix C of</p> <p>6 your report?</p> <p>7 MR. FROST: Objection.</p> <p>8 A. As I said, I didn't go through</p> <p>9 them, I didn't assess the methodology. I</p> <p>10 know that there are others that look at that</p> <p>11 specifically and look at the methodology and</p> <p>12 the conclusions of those testings.</p> <p>13 BY MR. SOILEAU:</p> <p>14 Q. Right. But you oversaw the</p> <p>15 design and creation of Appendix C. You told</p> <p>16 me that earlier, right?</p> <p>17 A. Yes, that's correct.</p> <p>18 Q. Does Appendix C include in</p> <p>19 those charts any positive findings on</p> <p>20 asbestos?</p> <p>21 MR. FROST: Objection.</p> <p>22 BY MR. SOILEAU:</p> <p>23 Q. You know, in the testing.</p> <p>24 A. As I said, there is asbestos</p>	<p>1 that was used in those, and I believe there</p> <p>2 are others who do that and -- who do that.</p> <p>3 BY MR. SOILEAU:</p> <p>4 Q. Okay, Doctor. Let's return now</p> <p>5 to the IARC monograph that we had before our</p> <p>6 last break, Tuttle Exhibit 34. Let's see if</p> <p>7 I can do this this time without losing my</p> <p>8 place.</p> <p>9 So I've turned to page 294 of</p> <p>10 Tuttle Exhibit 34, and I'm on Section 5,</p> <p>11 Evaluation. And I'm looking at the second</p> <p>12 sentence of that section, Evaluation. It</p> <p>13 says, quote: "Asbestos causes mesothelioma</p> <p>14 and cancer of the lung, larynx and ovary,"</p> <p>15 closed quote.</p> <p>16 Do you see that statement in</p> <p>17 the IARC monograph?</p> <p>18 A. Yes, I see that statement.</p> <p>19 Q. Do you agree with that</p> <p>20 statement?</p> <p>21 A. As I said previously, I'm aware</p> <p>22 that IARC has found that exposure to high</p> <p>23 occupational levels of asbestos was</p> <p>24 associated with ovarian cancer.</p>



Kelly Tuttle, Ph.D.

Page 370	Page 372
<p>1 Q. Yes, Doctor, but I'm not asking 2 you if IARC said that or if you are aware 3 that IARC said that. I'm asking you, as a 4 toxicologist, an expert witness put forward 5 in this case on behalf of Johnson &amp; Johnson, 6 if you agree that asbestos causes 7 mesothelioma and cancer of the lung, larynx 8 and ovary? 9 MR. FROST: Objection, form. 10 A. Well, again, as I said 11 previously, I'm aware that IARC has stated 12 that high occupational exposures to asbestos 13 is associated with ovarian cancer. In this 14 particular -- I was retained to look at the 15 body of evidence regarding talcum powder and 16 ovarian cancer. 17 BY MR. SOILEAU: 18 Q. What level of -- well, let me 19 ask you this. 20 Can we agree that there's no 21 safe level of asbestos for talcum powder 22 products? 23 MR. FROST: Objection. 24 ///</p>	<p>1 cleavage. 2 Q. That was in Mr. Moore's 3 deposition. 4 MR. FROST: Objection. 5 BY MR. SOILEAU: 6 Q. Well, we haven't talked about 7 it today. 8 A. No, you're correct, we haven't 9 discussed -- 10 Q. Have you done any work on that 11 for Johnson &amp; Johnson? 12 MR. FROST: Objection. 13 A. No, I have not. 14 BY MR. SOILEAU: 15 Q. Okay. All right. Go ahead, 16 I'm sorry. 17 A. I'm just saying that in regards 18 to my report and the research I've done, I've 19 been looking at the scientific evidence 20 regarding talcum powder and the causal 21 association with ovarian cancer and whether 22 the scientific evidence supports it. 23 I'm aware that IARC has, as I 24 stated previously, found that high</p>
Page 371	Page 373
<p>1 BY MR. SOILEAU: 2 Q. Do you agree with that 3 statement? There is no safe level of 4 asbestos in the talcum powder products? 5 MR. FROST: Objection. 6 BY MR. SOILEAU: 7 Q. For Johnson &amp; Johnson? 8 MR. FROST: Still objection. 9 A. Well, again, you know, we were 10 discussing earlier the Global Harmonization 11 Standard and the EPA guidelines that have 12 definitions regarding whether a material is 13 considered asbestos-containing or not, and 14 then we also briefly discussed fibrous talc, 15 you know, and we haven't discussed other 16 things. 17 I know there's been some 18 discussion regarding the methodology of, you 19 know, cleavage fragments in elongated 20 particles as opposed to asbestos. 21 BY MR. SOILEAU: 22 Q. Wait. You said cleavage. We 23 didn't talk cleavage. 24 A. You're right, we didn't discuss</p>	<p>1 occupational exposure levels of asbestos is 2 associated with ovarian cancer, but I have 3 not, you know, gone into the data regarding 4 asbestos, especially occupational levels of 5 exposure. I summarize it briefly in my 6 report. 7 Q. Does asbestos cause ovarian 8 cancer, Doctor? 9 MR. FROST: Objection, asked 10 and answered. 11 MR. SOILEAU: If there was an 12 answer in all of that, I promise you, 13 I didn't hear it and I lost it. 14 BY MR. SOILEAU: 15 Q. I mean, do you have an opinion? 16 You're a toxicologist. You're here. We're 17 talking about ovarian cancer. You knew we 18 were going to talk about ovarian cancer, and 19 you knew asbestos is an issue. You did the 20 Appendix C. You've seen Longo and Rigler and 21 you talk about asbestos in your report. 22 Can asbestos cause ovarian 23 cancer, Doctor? 24 MR. FROST: Objection, form.</p>

Kelly Tuttle, Ph.D.

<p style="text-align: right;">Page 374</p> <p>1 A. Well, and again, you know, IARC 2 has certainly stated that heavy occupational 3 exposures to asbestos are associated with 4 ovarian cancer. 5 BY MR. SOILEAU: 6 Q. Do you believe that's true? 7 A. I believe that is what IARC has 8 stated. For my -- but for my intents and 9 purposes, I'm looking at talcum powder in 10 ovarian cancer, and as you discussed, we were 11 talking about asbestos testing with talcum 12 powder. 13 But the scientific evidence 14 regarding talcum powder, if it does contain 15 asbestos, which as I stated previously, there 16 are others who get into that in more detail 17 than I do, all the epidemiological studies 18 and all the testing that's been done on the 19 talcum powder product would include any 20 materials that were included in the product, 21 including -- you know, if -- so if asbestos 22 was shown to be present, it would be included 23 in those studies. 24 Q. I was asking if it caused -- if</p>	<p style="text-align: right;">Page 376</p> <p>1 the ovary? 2 MR. FROST: Objection. Outside 3 of the opinions being rendered by this 4 witness. 5 A. So again, I was not asked to 6 look at the causal association between 7 occupational exposures to asbestos and 8 ovarian cancer. I was asked to look at the 9 causal association between talcum powder 10 exposure and ovarian cancer and whether 11 there's scientific evidence to support it. 12 BY MR. SOILEAU: 13 Q. Well, you knew that asbestos in 14 the talcum powder products is an issue, don't 15 you? 16 MR. FROST: Objection. 17 A. Well, as I said, I am aware 18 that there's been testing. I'm aware the FDA 19 has tested Johnson &amp; Johnson's talcum powder 20 and shown there was no asbestos, and I'm 21 aware that there is other -- there are other 22 experts in this litigation that look at that 23 in greater detail than I have. 24 ///</p>
<p style="text-align: right;">Page 375</p> <p>1 asbestos caused ovarian cancer, but I tell 2 you what, I give up. I don't think I can get 3 an answer. 4 Let me ask you this: If it 5 does, how does it get there? 6 MR. FROST: Objection. 7 A. Again, I was looking -- I've 8 been looking at talcum powder and ovarian 9 cancer. I'm aware that IARC has classified 10 it. I have not done research into the 11 occupational levels of exposure in ovarian -- 12 in asbestos and ovarian cancer. 13 BY MR. SOILEAU: 14 Q. Doesn't that trouble you? 15 MR. FROST: Objection. 16 BY MR. SOILEAU: 17 Q. Do you know how asbestos could 18 cause ovarian cancer? 19 MR. FROST: Objection. 20 BY MR. SOILEAU: 21 Q. However -- if it's 22 occupational, if it's heavy, if it's asbestos 23 workers, if they're cutting asbestos 24 insulation, how does asbestos find its way to</p>	<p style="text-align: right;">Page 377</p> <p>1 BY MR. SOILEAU: 2 Q. Then you must know it's an 3 issue in the case. 4 MR. FROST: Objection. 5 BY MR. SOILEAU: 6 Q. Why would we be talking about 7 it if it's not an issue in the case? 8 MR. FROST: Objection. 9 A. But again, regarding 10 establishing the scientific literature, if 11 you assume that the Johnson &amp; Johnson talcum 12 powder products or that talcum powder 13 contains asbestos, then all the studies that 14 look at talcum powder in epidemiological 15 studies or in other scenarios, then they 16 would contain the hypothetical asbestos as 17 opposed to -- and would have it -- so, 18 therefore, it's included in that scientific 19 literature. 20 BY MR. SOILEAU: 21 Q. I'm not sure if you're not 22 hearing my question or not answering it 23 despite hearing it, but I need to ask again. 24 If we assume that asbestos can</p>

Kelly Tuttle, Ph.D.

<p style="text-align: right;">Page 378</p> <p>1 cause ovarian cancer, how does it get there?</p> <p>2 MR. FROST: Same objections as</p> <p>3 I lodged before.</p> <p>4 A. And again, I did not research</p> <p>5 that in -- for this particular thing</p> <p>6 regarding asbestos, so I -- I don't know. I</p> <p>7 can't speak to it.</p> <p>8 BY MR. SOILEAU:</p> <p>9 Q. Does it?</p> <p>10 MR. FROST: Objection.</p> <p>11 A. Again, I didn't research it. I</p> <p>12 can't speak to it.</p> <p>13 BY MR. SOILEAU:</p> <p>14 Q. The fact that asbestos is a</p> <p>15 cause of ovarian cancer, doesn't that tell</p> <p>16 you as a toxicologist that it's making its</p> <p>17 way to the ovary?</p> <p>18 MR. FROST: Objection.</p> <p>19 A. Again, as I said before, I know</p> <p>20 that IARC has found that heavy occupational</p> <p>21 exposures are associated with ovarian cancer.</p> <p>22 I was asked to evaluate the science regarding</p> <p>23 perineal exposure to talcum powder and</p> <p>24 ovarian cancer, not the body of science</p>	<p style="text-align: right;">Page 380</p> <p>1 repeat the question for me, please?</p> <p>2 MR. SOILEAU: Sure.</p> <p>3 BY MR. SOILEAU:</p> <p>4 Q. Does it matter to you if the</p> <p>5 talcum powder products, including the baby</p> <p>6 powder that you're using with your newborn</p> <p>7 son, contains asbestos?</p> <p>8 MR. FROST: Objections.</p> <p>9 MS. WOODS: Objection.</p> <p>10 THE WITNESS: I'm sorry?</p> <p>11 BY MR. SOILEAU:</p> <p>12 Q. Does it matter to you if this</p> <p>13 product has asbestos in it?</p> <p>14 MR. FROST: Objection.</p> <p>15 A. Well, again, in looking at the</p> <p>16 scientific evidence, if we assume that the</p> <p>17 product has asbestos in it, which again,</p> <p>18 there has been testing that's shown it does</p> <p>19 not, and there are others involved that get</p> <p>20 into the testing and the methodologies in</p> <p>21 more detail.</p> <p>22 But if we assume -- and I</p> <p>23 even -- I think I state this in my report,</p> <p>24 but even if we assume that the product is</p>
<p style="text-align: right;">Page 379</p> <p>1 regarding occupational exposures to asbestos</p> <p>2 and ovarian cancer.</p> <p>3 BY MR. SOILEAU:</p> <p>4 Q. As a toxicologist, 255 hours of</p> <p>5 looking at this issue, your background,</p> <p>6 training and experience and the fact that</p> <p>7 you've worked in asbestos litigation before,</p> <p>8 doesn't it matter to you if there is asbestos</p> <p>9 in the talcum powder products?</p> <p>10 MR. FROST: Objection.</p> <p>11 Certainly outside the scope of this</p> <p>12 witness' testimony she's giving here</p> <p>13 today on behalf of Johnson &amp; Johnson.</p> <p>14 MR. SOILEAU: I don't know why</p> <p>15 because she offers an opinion about</p> <p>16 causation. She has asbestos in her</p> <p>17 report. She offers a causation</p> <p>18 discussion in her report and she's got</p> <p>19 an appendix, which is some 60-plus</p> <p>20 pages, I think, of a chart that</p> <p>21 includes asbestos testing.</p> <p>22 But in any event, subject to</p> <p>23 the objection.</p> <p>24 THE WITNESS: Okay. Can you</p>	<p style="text-align: right;">Page 381</p> <p>1 asbestos-containing, when we look at the</p> <p>2 scientific literature regarding talcum powder</p> <p>3 and ovarian cancer, that would include any</p> <p>4 hypothetical components that were present in</p> <p>5 the talcum powder.</p> <p>6 BY MR. SOILEAU:</p> <p>7 Q. Does that mean it matters to</p> <p>8 you or it doesn't matter to you?</p> <p>9 MR. FROST: Objection.</p> <p>10 A. It means that if the talcum</p> <p>11 powder -- you know, again, if we assume that</p> <p>12 it does contain asbestos, which again, there</p> <p>13 has been testing to show consistently that it</p> <p>14 does not, that all the studies that are</p> <p>15 assessing the potential causal relationship</p> <p>16 between perineal talcum powder exposure and</p> <p>17 ovarian cancer would also include any</p> <p>18 asbestos that was hypothetically present in</p> <p>19 the talcum powder.</p> <p>20 BY MR. SOILEAU:</p> <p>21 Q. So it does matter or it doesn't</p> <p>22 matter --</p> <p>23 MR. FROST: Objection.</p> <p>24 ///</p>

96 (Pages 378 to 381)

Kelly Tuttle, Ph.D.

<p style="text-align: right;">Page 382</p> <p>1 BY MR. SOILEAU:</p> <p>2 Q. -- to your analysis and your</p> <p>3 opinions in this case, Doctor?</p> <p>4 MR. FROST: Objection.</p> <p>5 A. Again, any -- any of the</p> <p>6 studies that look at talcum powder -- excuse</p> <p>7 me.</p> <p>8 If we assume that the talcum</p> <p>9 powder -- that Johnson &amp; Johnson's baby</p> <p>10 powder or Shower to Shower products contained</p> <p>11 asbestos, even though there has been testing</p> <p>12 that showed they do not, even if we assume it</p> <p>13 is there, then the scientific data regarding</p> <p>14 talcum powder would include any components</p> <p>15 that were present in the talcum powder when</p> <p>16 assessing the potential for a causal</p> <p>17 association between talcum powder perineally</p> <p>18 and ovarian cancer.</p> <p>19 BY MR. SOILEAU:</p> <p>20 Q. Does inhalation of talcum</p> <p>21 powder products offer a pathway to the</p> <p>22 ovaries?</p> <p>23 MR. FROST: Objection.</p> <p>24 A. I don't know specifically.</p>	<p style="text-align: right;">Page 384</p> <p>1 emergency response and nonlitigation</p> <p>2 consulting.</p> <p>3 Q. Right. Were you involved in</p> <p>4 the BP project at all?</p> <p>5 A. No, I was not.</p> <p>6 Q. Are you aware of any</p> <p>7 controversy involving CTEH's role in the BP</p> <p>8 spill?</p> <p>9 MR. FROST: Objection.</p> <p>10 A. Very generally, I'm aware of a</p> <p>11 news article that I believe CTEH drafted a</p> <p>12 response to. I don't know any, yeah, real</p> <p>13 specifics. I wasn't involved. It was before</p> <p>14 my time with the company.</p> <p>15 BY MR. SOILEAU:</p> <p>16 Q. In the materials that you</p> <p>17 presented with your report and your report, I</p> <p>18 think, in speaking of qualifications, says</p> <p>19 that CTEH is associated with the University</p> <p>20 of Arkansas Medical Sciences BioVentures</p> <p>21 program.</p> <p>22 Do you recall that?</p> <p>23 A. Yes, I believe that that's</p> <p>24 stated in my report.</p>
<p style="text-align: right;">Page 383</p> <p>1 BY MR. SOILEAU:</p> <p>2 Q. Okay. You discuss animal</p> <p>3 models of talc exposure and toxicity at</p> <p>4 pages 17 and 18 of your report, correct?</p> <p>5 A. Yes.</p> <p>6 Q. You have three paragraphs, just</p> <p>7 three paragraphs there.</p> <p>8 A. Yes, that's correct.</p> <p>9 Q. Isn't animal study -- well,</p> <p>10 first, isn't that an early area of focus for</p> <p>11 you?</p> <p>12 MR. FROST: Objection.</p> <p>13 A. I did animal studies during my</p> <p>14 Ph.D., yes.</p> <p>15 BY MR. SOILEAU:</p> <p>16 Q. Did you ever study veterinary</p> <p>17 science?</p> <p>18 A. My bachelor's is in veterinary</p> <p>19 science, yes.</p> <p>20 Q. That's what I was referring to.</p> <p>21 Your work now with CTEH, is it</p> <p>22 generally emergency response?</p> <p>23 A. Yes, I think I stated earlier</p> <p>24 that the majority of my work with CTEH is</p>	<p style="text-align: right;">Page 385</p> <p>1 Q. CTEH is not associated with the</p> <p>2 University of Arkansas Medical Sciences</p> <p>3 school, is it?</p> <p>4 A. So it's associated with their</p> <p>5 BioVentures program, and again, this is</p> <p>6 obviously before my time, so I can only speak</p> <p>7 in generalities, but the -- it was originally</p> <p>8 a start-off from professors at the University</p> <p>9 of Arkansas.</p> <p>10 Q. Well, isn't it true that the</p> <p>11 BioVentures program is a program that</p> <p>12 generates spinoff companies that are in the</p> <p>13 same area generally that CTEH is in?</p> <p>14 A. I couldn't speak to other</p> <p>15 companies that went through the BioVentures</p> <p>16 program. I didn't go to the University of</p> <p>17 Arkansas, and as I said, that was years</p> <p>18 before I joined CTEH.</p> <p>19 Q. Have you heard the phrase</p> <p>20 "spinoff companies"?</p> <p>21 A. I --</p> <p>22 Q. I'm sorry, I apologize. Just</p> <p>23 to be more clear, in connection with this</p> <p>24 relationship of CTEH and the BioVentures</p>

97 (Pages 382 to 385)

Kelly Tuttle, Ph.D.

Page 386	Page 388
<p>1 program?</p> <p>2 A. Again, I don't know that I have</p> <p>3 specifically.</p> <p>4 Q. All right. Take a look at that</p> <p>5 document, tell me if you've seen that before.</p> <p>6 That may be a website printout, by the way,</p> <p>7 if it helps you.</p> <p>8 THE REPORTER: Is that marked?</p> <p>9 THE WITNESS: 35.</p> <p>10 MR. SOILEAU: Yes, 35.</p> <p>11 (Whereupon, Deposition Exhibit</p> <p>12 Tuttle-35, Listing of BioVentures</p> <p>13 Spinoff Companies, was marked for</p> <p>14 identification.)</p> <p>15 BY MR. SOILEAU:</p> <p>16 Q. Have you seen that before?</p> <p>17 A. No, I have not.</p> <p>18 Q. All right. Let's go back to</p> <p>19 the animal studies for a moment. When you</p> <p>20 wrote your report, you had Dr. Plunkett's</p> <p>21 report, didn't you, Doctor?</p> <p>22 A. Yes, I did.</p> <p>23 Q. Do you know whether you</p> <p>24 considered -- well, did you identify the</p>	<p>1 MR. FROST: Objection.</p> <p>2 BY MR. SOILEAU:</p> <p>3 Q. Is that what you're telling me?</p> <p>4 A. As I've said, the in vitro,</p> <p>5 animal, in vivo or human studies all play a</p> <p>6 role in toxicological research.</p> <p>7 Q. Equally?</p> <p>8 A. It would depend on the area of</p> <p>9 toxicology that you're discussing as far as</p> <p>10 which one would be used or encountered more</p> <p>11 frequently.</p> <p>12 Q. Are you familiar with a study</p> <p>13 called Shim, S-H-I-M, 2015, that is noted in</p> <p>14 Dr. Plunkett's report, paragraph 63, page 43?</p> <p>15 A. I -- if you could -- you'd have</p> <p>16 to provide me where she refers to it in</p> <p>17 Dr. Plunkett's report.</p> <p>18 Q. Right. Okay. Well, I'm not</p> <p>19 going to take the time to do that right now.</p> <p>20 We've had some long answers and we're going</p> <p>21 to run out of time shortly.</p> <p>22 Can we agree that oxidative</p> <p>23 stress produced by talc is evidence of</p> <p>24 toxicity of talc?</p>
Page 387	Page 389
<p>1 animal studies that Dr. Plunkett cited and</p> <p>2 discussed in her report? In other words, did</p> <p>3 you take her report and see what studies she</p> <p>4 had looked at?</p> <p>5 A. I certainly looked at the</p> <p>6 references cited in Dr. Plunkett's report. I</p> <p>7 don't recall how in depth I went regarding</p> <p>8 animal studies as you -- we noted previously.</p> <p>9 I just briefly touch on animal models of talc</p> <p>10 exposure and toxicity in section 7.1.</p> <p>11 Q. Right. That struck me. Isn't</p> <p>12 it true that animal studies are sort of the</p> <p>13 foundation of toxicology?</p> <p>14 MR. FROST: Objection.</p> <p>15 A. There are a lot of different --</p> <p>16 you know, the foundation of toxicology is the</p> <p>17 dose makes the poison. In vitro animal</p> <p>18 studies and epidemiological or human studies</p> <p>19 all are encompassed in the science of</p> <p>20 toxicology and toxicological research.</p> <p>21 BY MR. SOILEAU:</p> <p>22 Q. So it's your testimony that</p> <p>23 toxicologists deal with in vitro, in vivo and</p> <p>24 epidemiological studies equally?</p>	<p>1 MR. FROST: Objection.</p> <p>2 BY MR. SOILEAU:</p> <p>3 Q. If we have a study that shows</p> <p>4 oxidative stress produced by talc, is that</p> <p>5 evidence of toxicity for talc?</p> <p>6 MR. FROST: Objection.</p> <p>7 A. It would -- it would depend on</p> <p>8 the study. As I mentioned earlier, the</p> <p>9 inflammatory response and things like that</p> <p>10 are normal processes in the body, and I would</p> <p>11 need to see the study and what they were</p> <p>12 looking at and what the conclusions were</p> <p>13 to -- and what avenue you're discussing</p> <p>14 regarding mechanism of toxicity.</p> <p>15 BY MR. SOILEAU:</p> <p>16 Q. How about you look at your</p> <p>17 reference materials and see if you discuss or</p> <p>18 include in your reference materials a report</p> <p>19 and animal study by Shim, S-H-I-M, from 2015.</p> <p>20 A. No, I do not.</p> <p>21 Q. What about Radic, R-A-D-I-C, a</p> <p>22 1988 study cited by Dr. Plunkett at page 39</p> <p>23 of her report, paragraph 59, for suppression</p> <p>24 of immune system function? Do you include</p>

98 (Pages 386 to 389)



Kelly Tuttle, Ph.D.

Page 390	Page 392
<p>1 that in your reference materials?</p> <p>2 A. No, I do not.</p> <p>3 Q. Is suppression of the immune</p> <p>4 system function evidence of toxicity?</p> <p>5 A. Again, it depends. That's a</p> <p>6 very general term. There's not one universal</p> <p>7 mechanism of toxicity.</p> <p>8 Q. Well, can we agree that if</p> <p>9 Dr. Plunkett cited the Radic 1988 study in</p> <p>10 her report, that you had notice of this</p> <p>11 report, this study, and an opportunity to</p> <p>12 look at both Shim and Radic before you</p> <p>13 rendered your report?</p> <p>14 MR. FROST: Objection.</p> <p>15 A. Again, my report, my goal was</p> <p>16 to assess the scientific literature regarding</p> <p>17 the potential for perineal talc exposure and</p> <p>18 causal association with ovarian cancer. I</p> <p>19 read Dr. Plunkett's report. As I said, I</p> <p>20 looked at the data Dr. Plunkett cites. I</p> <p>21 don't claim to have cited every reference</p> <p>22 that Dr. Plunkett cites, and my specific</p> <p>23 addresses to Dr. Plunkett are listed herein</p> <p>24 and I only briefly touch on animal models or</p>	<p>1 thousands of studies that are out there.</p> <p>2 I'm asking you specifically</p> <p>3 about studies that Dr. Plunkett had in her</p> <p>4 report that was provided to you as noted at</p> <p>5 page 2 of your report, and you said to me,</p> <p>6 quote, "As I said, I looked at the data</p> <p>7 Dr. Plunkett cites," period. "I don't claim</p> <p>8 to have cited every reference that</p> <p>9 Dr. Plunkett cites." And you continue. Your</p> <p>10 testimony will speak for itself.</p> <p>11 I'm just trying to find out if</p> <p>12 you did, as you said a moment ago, look at</p> <p>13 the data that Dr. Plunkett cites, including</p> <p>14 Shim and Radic.</p> <p>15 MR. FROST: Objection.</p> <p>16 A. So again, you know, the</p> <p>17 references that I cite in my report are the</p> <p>18 references that I rely upon in my report.</p> <p>19 BY MR. SOILEAU:</p> <p>20 Q. But not necessarily everything</p> <p>21 you looked at.</p> <p>22 A. Well, you know, we discussed</p> <p>23 that previously.</p> <p>24 Q. Right.</p>
Page 391	Page 393
<p>1 the animal studies regarding talc exposure.</p> <p>2 BY MR. SOILEAU:</p> <p>3 Q. This is a point that we</p> <p>4 discussed a bit earlier in your deposition.</p> <p>5 You said just now you looked at the data</p> <p>6 Dr. Plunkett cites.</p> <p>7 Does that mean that if</p> <p>8 Dr. Plunkett cited Shim and Radic, that you</p> <p>9 would have looked at those studies?</p> <p>10 MR. FROST: Objection.</p> <p>11 A. I -- again, I don't claim -- I</p> <p>12 think I just said that I don't claim to have</p> <p>13 pulled every single reference that</p> <p>14 Dr. Plunkett cites. My address -- you know,</p> <p>15 my references to Dr. Plunkett's report are in</p> <p>16 my report and what I address specifically, I</p> <p>17 did not get into the scientific literature</p> <p>18 regarding an exhaustive search around animal</p> <p>19 studies. As I said, we only briefly -- I</p> <p>20 only briefly touch on talc exposure in animal</p> <p>21 studies.</p> <p>22 BY MR. SOILEAU:</p> <p>23 Q. I understand that, but no, no,</p> <p>24 no, no. I'm not asking you about the</p>	<p>1 A. In looking at Dr. Plunkett's</p> <p>2 report, my -- the things that I address in</p> <p>3 her report are listed in my report. I</p> <p>4 don't -- and again, I don't get into a</p> <p>5 detailed discussion of the in vivo studies</p> <p>6 regarding talc exposure.</p> <p>7 There's already a lot of</p> <p>8 evidence in the epidemiological studies in</p> <p>9 the human studies that I did not spend a</p> <p>10 large amount of time in the scientific</p> <p>11 research looking at the animal studies or the</p> <p>12 in vitro studies, which are useful as we were</p> <p>13 talking about earlier, but for causation</p> <p>14 assessment analyses, you know, the human</p> <p>15 studies are what primarily -- what I</p> <p>16 emphasized in my report.</p> <p>17 Q. Why not?</p> <p>18 MR. FROST: Objection.</p> <p>19 BY MR. SOILEAU:</p> <p>20 Q. So why not?</p> <p>21 MR. FROST: Why not what? I</p> <p>22 don't understand what the why not is</p> <p>23 to.</p> <p>24 MR. SOILEAU: Well, I know,</p>

Kelly Tuttle, Ph.D.

Page 394	Page 396
<p>1 it's buried in those long answers, but</p> <p>2 she said "I don't get into a detailed</p> <p>3 discussion of the in vivo studies</p> <p>4 regarding talc exposure."</p> <p>5 BY MR. SOILEAU:</p> <p>6 Q. And that's my question: Why</p> <p>7 not?</p> <p>8 You also said, "I did not spend</p> <p>9 a large amount of time in the scientific</p> <p>10 research looking at the animal studies."</p> <p>11 Why not?</p> <p>12 A. Because again, I was asked to</p> <p>13 assess is the scientific literature about a</p> <p>14 causal association, and while in vivo studies</p> <p>15 and in vitro studies are useful for looking</p> <p>16 at various aspects of toxicology, the</p> <p>17 epidemiological studies and the studies that</p> <p>18 I spend -- you know, those are the ones that</p> <p>19 we use as far as epidemiological and</p> <p>20 human-based, if they're available, for</p> <p>21 establishing a causal association or seeing</p> <p>22 if the data supports a causal association.</p> <p>23 Q. Let's do a couple more from</p> <p>24 Dr. Plunkett's report. Beck 1987, for the</p>	<p>1 BY MR. SOILEAU:</p> <p>2 Q. Are animal studies -- can we</p> <p>3 take animal -- mammalian animal studies and</p> <p>4 apply those to humans? That is, if we see a</p> <p>5 toxic effect in mammalian species, is it fair</p> <p>6 to expect that we will see those in humans as</p> <p>7 well?</p> <p>8 A. No, you need more information.</p> <p>9 As I said before, animal studies are</p> <p>10 certainly useful tools, but animal studies</p> <p>11 are -- you know, animals do not share</p> <p>12 identical mechanisms or physiological impacts</p> <p>13 to humans.</p> <p>14 And so you can't just say that</p> <p>15 if it exerts a toxic effect in an animal that</p> <p>16 it will assert a toxic effect in a human.</p> <p>17 You would need more research and more</p> <p>18 information.</p> <p>19 Q. What good are animal studies if</p> <p>20 we can't apply them to humans?</p> <p>21 MR. FROST: Objection.</p> <p>22 A. Well, again, what I said was</p> <p>23 that you need more information as far as</p> <p>24 animal studies. Animal studies are useful,</p>
Page 395	Page 397
<p>1 record, it's at page 39 of Dr. Plunkett's</p> <p>2 report, paragraph 59. It's cited for</p> <p>3 macrophage phagocytosis inhibited and</p> <p>4 elevated enzyme levels.</p> <p>5 A. And what was the question?</p> <p>6 Q. Did you look at the Beck '87</p> <p>7 reference list?</p> <p>8 A. Again, I don't cite a Beck</p> <p>9 article in my report.</p> <p>10 Q. Okay. Can you agree that</p> <p>11 elevated enzyme levels is evidence of</p> <p>12 toxicity?</p> <p>13 MR. FROST: Objection.</p> <p>14 A. Again, it would depend, as we</p> <p>15 discussed previously, there's not a universal</p> <p>16 mechanism of toxicity. I would need to see</p> <p>17 the study and see what the parameters are,</p> <p>18 what they're looking at.</p> <p>19 BY MR. SOILEAU:</p> <p>20 Q. If, in a human body, the</p> <p>21 macrophage phagocytosis is inhibited, is that</p> <p>22 evidence of toxicity?</p> <p>23 MR. FROST: Objection.</p> <p>24 A. Again, it depends.</p>	<p>1 they help us understand different things</p> <p>2 depending on the questions asked, but you</p> <p>3 cannot just take a single animal study and</p> <p>4 directly apply it to human toxicity or</p> <p>5 human -- human information.</p> <p>6 BY MR. SOILEAU:</p> <p>7 Q. And you're saying animal. I</p> <p>8 just want to make sure it's clear that I'm</p> <p>9 asking you specifically about mammalian</p> <p>10 studies. Is that understood?</p> <p>11 A. Yes.</p> <p>12 Q. Okay. But your testimony is</p> <p>13 the same, right?</p> <p>14 A. Well, again, as I said, you</p> <p>15 know, animal studies are useful. As far as</p> <p>16 the application to human, you would need more</p> <p>17 information there. You know, as I stated</p> <p>18 before, the anatomy and physiology of animals</p> <p>19 is not identical to human anatomy and</p> <p>20 physiology.</p> <p>21 Q. What animal model is the most</p> <p>22 appropriate to study ovarian cancer?</p> <p>23 MR. FROST: Objection.</p> <p>24 ///</p>

100 (Pages 394 to 397)

Kelly Tuttle, Ph.D.

Page 398	Page 400
<p>1 BY MR. SOILEAU: 2 Q. Do you know? 3 A. I briefly discussed some of the 4 ovarian -- models, animal models of ovarian 5 cancer. It would depend on what question you 6 were wanting to answer. 7 Q. Well, I'm just -- if I -- if 8 the object is to study ovarian cancer, which 9 model is the most appropriate? 10 MR. FROST: Objection. 11 A. Again, it would depend on the 12 hypothesis that's being tested. 13 BY MR. SOILEAU: 14 Q. Let me show you what I'm going 15 to mark as Tuttle Exhibit 36. 16 (Whereupon, Deposition Exhibit 17 Tuttle-36, NTP Study, Toxicology and 18 Carcinogenesis Studies of Talc, was 19 marked for identification.) 20 BY MR. SOILEAU: 21 Q. Is this the NTP study, Doctor, 22 that you reference in your report? 23 A. I'm just double-checking. Yes, 24 I believe it is.</p>	<p>1 MR. SOILEAU: It's on page -- 2 MR. FROST: 54. 3 MR. SOILEAU: -- 54. Thank 4 you. 5 BY MR. SOILEAU: 6 Q. I'm interested in the language 7 here that begins within the paragraph to the 8 left below the chart. It says: The interim 9 evaluations in the NTP talc study clearly 10 demonstrate a progressive impairment of 11 homeostatic growth regulation in the areas of 12 chronic inflammation and fibrosis associated 13 with talc deposition in rats. 14 You're aware of this finding? 15 A. As I said, I've read this 16 article or, I'm sorry, I've read this 17 research by the NTP. I don't know 18 specifically that it's a finding. Like you 19 say, it's a large document, and there have 20 been several documents that I've -- 21 Q. There have been several -- 22 A. -- read. 23 Q. Several whats? I didn't hear 24 you.</p>
Page 399	Page 401
<p>1 Q. Very well. 2 I know you have a number of 3 things to say about this report, but I want 4 to ask you: Isn't it true -- well, first, do 5 you know what an interim evaluation is? 6 A. I guess it would depend on the 7 context, but -- 8 Q. Well, in the context of an NTP 9 study like this one I just put in front of 10 you. 11 A. Do they -- I mean an interim 12 evaluation, I guess I'd have to see it used 13 in the context. Like I said, I know what 14 interim and evaluation mean, but as far as if 15 it's a preliminary study or if the results 16 are not finished yet or what they mean when 17 they say interim evaluation. 18 Q. Well, what about if I say 19 interim sacrifice, does that help? 20 A. No, that doesn't. 21 Q. Okay. Turn to page 54 of this 22 exhibit, which I have marked as Tuttle 36. 23 MR. ZELLERS: I'm sorry, what 24 page, Counselor?</p>	<p>1 A. Oh, I said there have been a 2 lot of articles that I've been reading in 3 accordance with this. 4 Q. Let's just focus on this 5 sentence then. It's not to be a memory test 6 so much. Do you know first what interim 7 evaluations mean here? 8 You said context before. You 9 know what interim means, you know what 10 evaluation means, but do you know what is 11 meant by interim evaluations as used here at 12 page 54 of this NTP study? 13 A. Judging from what it's saying 14 here, it sounds like it's -- you know, and 15 again, I'm not the author of this document, 16 so I'm merely having to base this on a single 17 sentence, again, not -- not the entire 18 context of the document. 19 But it looks like there -- 20 maybe another word would be preliminary 21 evaluations or evaluations in the ongoing -- 22 the ongoing study. 23 Q. Okay. And they say that the 24 interim evaluations in the NTP talc study</p>

101 (Pages 398 to 401)

Kelly Tuttle, Ph.D.

<p style="text-align: right;">Page 402</p> <p>1 clearly demonstrate a progressive impairment</p> <p>2 of homeostatic growth regulation in the areas</p> <p>3 of chronic inflammation and fibrosis</p> <p>4 associated with talc deposition in rats.</p> <p>5 What does that mean to you,</p> <p>6 Doctor, as a toxicologist?</p> <p>7 A. Well, again, taking the one</p> <p>8 statement, you know, out of this very</p> <p>9 substantial document, and there's about five</p> <p>10 pages of discussion and conclusions that</p> <p>11 precede this particular paragraph, there</p> <p>12 are -- so I don't know that I can speak to</p> <p>13 what the authors are specifically saying</p> <p>14 here. There's...</p> <p>15 Q. What is homeostatic growth</p> <p>16 regulation?</p> <p>17 A. Again, I don't feel</p> <p>18 comfortable. I don't think I can define that</p> <p>19 scientifically without having a reference in</p> <p>20 front of me. I don't want to misspeak.</p> <p>21 Q. Okay. I'm going to the next</p> <p>22 sentence. It says: Hyperplasia --</p> <p>23 hyperplasia of the alveolar epithelium.</p> <p>24 Do you know what hyperplasia</p>	<p style="text-align: right;">Page 404</p> <p>1 A. Well, I believe, if you look at</p> <p>2 the, actually, next sentence, we do have a</p> <p>3 definition as far as this NTP document</p> <p>4 regarding hyperplasia, where they say there</p> <p>5 was an increased number of cells.</p> <p>6 Q. What's that mean, Doctor?</p> <p>7 A. It would mean there's an</p> <p>8 increased number of cells in the alveolar</p> <p>9 regions that they were looking at in this</p> <p>10 particular study.</p> <p>11 Q. What's going on here? What's</p> <p>12 NTP seeing? Do you know?</p> <p>13 A. Hmm?</p> <p>14 Q. What is NTP seeing here in</p> <p>15 these results?</p> <p>16 A. NTPC?</p> <p>17 Q. NTP. What did I say?</p> <p>18 A. You said NTPC.</p> <p>19 Q. No. I'm sorry. I meant "see"</p> <p>20 as with observational.</p> <p>21 A. Oh.</p> <p>22 Q. Can you help me understand</p> <p>23 what's going on here in this section of this</p> <p>24 report from the National Toxicology Program,</p>
<p style="text-align: right;">Page 403</p> <p>1 is?</p> <p>2 A. Again, yes. As far as a</p> <p>3 definition, I wouldn't want to misspeak and</p> <p>4 misquote the scientific definition in the</p> <p>5 media -- or sorry, not in the media -- in the</p> <p>6 scientific literature.</p> <p>7 Q. How and why, if at all, is a</p> <p>8 finding of hyperplasia in the epithelium</p> <p>9 tissue that's evident at six months and that</p> <p>10 became more extensive and severe with</p> <p>11 duration of exposure significant to the</p> <p>12 issues we discuss here today, Doctor?</p> <p>13 A. Well, again, it would depend.</p> <p>14 In this particular study, it's talking about</p> <p>15 the lung alveolar and inhalational exposures.</p> <p>16 I would need to look at more information to</p> <p>17 determine whether it is applied here.</p> <p>18 As I said previously, I looked</p> <p>19 at the perineal application of talcum powder</p> <p>20 and the causal association with ovarian</p> <p>21 cancer.</p> <p>22 Q. Does hyperplasia have any</p> <p>23 relationship to carcinogenicity or the</p> <p>24 development of cancer?</p>	<p style="text-align: right;">Page 405</p> <p>1 a report that you cited?</p> <p>2 A. Again, without being able to</p> <p>3 refamiliarize myself with the report, just</p> <p>4 taking a couple of sentences in the</p> <p>5 discussions and conclusions, I -- I am afraid</p> <p>6 I can't help you as far as what is NTP, you</p> <p>7 know, looking at.</p> <p>8 As I said before, I've read the</p> <p>9 report, but I don't have a photographic</p> <p>10 memory, so I can't remember all the nuances</p> <p>11 in it and all the context.</p> <p>12 Q. Very well, Doctor.</p> <p>13 Let's go back to Exhibit 3.</p> <p>14 That is the Reference Manual on Scientific</p> <p>15 Evidence. You recall we discussed that</p> <p>16 earlier? I'm looking at page 646.</p> <p>17 Do you see the heading D,</p> <p>18 Extrapolation from Animal and Cell Research</p> <p>19 to Humans on page 646 of Tuttle Exhibit 3,</p> <p>20 the Reference Manual on Scientific Evidence?</p> <p>21 A. Yes, I see it.</p> <p>22 Q. Do you see the second sentence</p> <p>23 that says: In qualitative extrapolation, one</p> <p>24 can usually rely on the fact that a compound</p>

Kelly Tuttle, Ph.D.

<p style="text-align: right;">Page 406</p> <p>1 causing an effect in one mammalian species</p> <p>2 will cause it in another species, end of</p> <p>3 quote.</p> <p>4 Do you see that?</p> <p>5 A. I see that, where it states</p> <p>6 that, but again, I'd have to look at the rest</p> <p>7 of the paragraph and the rest of the section.</p> <p>8 Q. Sure. Do you agree with that</p> <p>9 statement, though?</p> <p>10 MR. FROST: Objection.</p> <p>11 A. Well, as I said before, and</p> <p>12 this is dealing in qualitative</p> <p>13 extrapolations --</p> <p>14 BY MR. SOILEAU:</p> <p>15 Q. It is.</p> <p>16 A. As I said previously, we would</p> <p>17 need more information in regards to an animal</p> <p>18 study and the extrapolation to humans.</p> <p>19 As I said previously, the</p> <p>20 anatomy and physiology in animals is not</p> <p>21 identical to that in humans, and there are --</p> <p>22 in fact, it says some different things down</p> <p>23 here about the mathematical depiction for</p> <p>24 pharmacokinetics and toxicokinetics for</p>	<p style="text-align: right;">Page 408</p> <p>1 you are -- you know, that animal and cell</p> <p>2 research is extremely useful to</p> <p>3 toxicologists, the extrapolation, you need</p> <p>4 more information than just a general -- if an</p> <p>5 adverse effect occurs in an animal study,</p> <p>6 that it will also occur in humans.</p> <p>7 BY MR. SOILEAU:</p> <p>8 Q. Do you know if -- if the</p> <p>9 Casarett text on toxicology that we talked</p> <p>10 about earlier in your deposition says two</p> <p>11 main principles underlie all descriptive</p> <p>12 animal toxicity testing; the first is that</p> <p>13 the effects produced by a compound in</p> <p>14 laboratory animals when properly qualified</p> <p>15 are applicable to humans. This premise</p> <p>16 applies to all of experimental biology and</p> <p>17 medicine.</p> <p>18 Does that sound familiar to</p> <p>19 you? I don't have -- I didn't bring this as</p> <p>20 an exhibit. I didn't know this was going to</p> <p>21 be an issue, but I have a copy of it here.</p> <p>22 Do you recognize that language?</p> <p>23 Two main principles underlie all descriptive</p> <p>24 animal toxicity testing; the first is that</p>
<p style="text-align: right;">Page 407</p> <p>1 extrapolating those kinds of studies to</p> <p>2 humans.</p> <p>3 Q. Doctor, isn't it true that this</p> <p>4 statement that I read stating: In</p> <p>5 qualitative extrapolation, one can usually</p> <p>6 rely on the fact that a compound causing an</p> <p>7 effect in one mammalian species will cause it</p> <p>8 in another species, is a basic principle of</p> <p>9 toxicology?</p> <p>10 MR. FROST: Objection.</p> <p>11 A. Well, again, as I've stated</p> <p>12 before, it would depend -- and again, this</p> <p>13 doesn't say an effect in one mammalian</p> <p>14 species will cause an effect in humans. It</p> <p>15 just states another species.</p> <p>16 BY MR. SOILEAU:</p> <p>17 Q. Well, that's certainly true.</p> <p>18 It also says this is a basic principle of</p> <p>19 toxicology, doesn't it? Right there?</p> <p>20 A. In the next sentence, yes, it</p> <p>21 states that.</p> <p>22 Q. Do you disagree with that?</p> <p>23 MR. FROST: Objection.</p> <p>24 A. Well, again, as I said, when</p>	<p style="text-align: right;">Page 409</p> <p>1 effects produced by a compound in laboratory</p> <p>2 animals when properly qualified are</p> <p>3 applicable to humans. This premise applies</p> <p>4 to all of experimental biology and medicine.</p> <p>5 A. Well, again, I don't have the</p> <p>6 textbook in front of me. You have put it on</p> <p>7 the overhead.</p> <p>8 Q. True, but --</p> <p>9 A. You do note that it says when</p> <p>10 properly -- if you'd put it back up there,</p> <p>11 please.</p> <p>12 Q. Sure. You see, I'm just</p> <p>13 showing it's Chapter 2, Principles of</p> <p>14 Toxicology, and I just want to show you that</p> <p>15 it's Chapter 2, Principles of Toxicology,</p> <p>16 from Casarett, whether you recognize it or</p> <p>17 not. I'll put it back up there for you.</p> <p>18 There you go.</p> <p>19 A. So as it says, when properly</p> <p>20 qualified. And as I say -- are applicable to</p> <p>21 humans. And as I said, when doing animal</p> <p>22 research, it is very useful to toxicologists,</p> <p>23 but to apply it to human studies, you -- to</p> <p>24 apply it to humans, there are -- you can't</p>



Kelly Tuttle, Ph.D.

<p style="text-align: right;">Page 410</p> <p>1 just -- I can't remember what the exact word 2 I used, but animal studies cannot just be 3 directly applied to humans. There is more 4 information that's needed, and as it states 5 here, it needs to be properly qualified. 6 Q. Isn't this statement in 7 Casarett that I am showing you consistent 8 with the statement from the reference manual 9 that we looked at a moment ago, page 646 of 10 Exhibit 3? 11 MR. FROST: Objection. 12 A. Well, again, as I said, the 13 extrapolation of animal and in vitro studies 14 to humans, you know, those studies are useful 15 for toxicologists, but there needs to be more 16 information when you're doing extrapolation 17 because the anatomy and physiology of animals 18 is not identical to that in humans. 19 BY MR. SOILEAU: 20 Q. Are you familiar with the 21 anatomy of ovaries in rats? 22 MR. FROST: Objection. 23 A. I'm vaguely familiar with the 24 anatomy. It's not something that I have done</p>	<p style="text-align: right;">Page 412</p> <p>1 individual cohort study that -- or each study 2 that I cite for me to be able to say 3 specifically. 4 Q. You can't tell me whether the 5 cohort studies include dose information as we 6 sit here? 7 MR. FROST: Objection. 8 BY MR. SOILEAU: 9 Q. The cohort studies discussed in 10 your report, cohort studies on talcum powder 11 products. 12 A. Well, as I said, we can look at 13 each individual study and my discussion on 14 them. There are some that attempt to 15 establish some dose information and some that 16 do not, but I have to look at each individual 17 study. 18 Q. By the way, this NTP study, 19 this discussion we were looking at, at 20 page 54, where it says: Hyperplasia was 21 evident at six months and became more 22 extensive and severe with duration of 23 exposure. 24 Does that sound like</p>
<p style="text-align: right;">Page 411</p> <p>1 research on. 2 BY MR. SOILEAU: 3 Q. You spend, I think, about 13 4 pages, which I'm calculating at about 20% of 5 the body of your expert report, dedicated to 6 epidemiology. 7 Does that surprise you or do 8 you realize that that much attention is paid 9 to epidemiology in your report? 10 A. I would have to count the pages 11 to confirm whether your numbers are accurate, 12 but I certainly -- as I stated previously, 13 the available scientific literature does have 14 epidemiological studies and the actual 15 examination of the potential association 16 between talcum powder use and ovarian cancer 17 in humans, and so that would certainly be 18 where I would -- you know, I spent a lot of 19 time in my scientific research. 20 Q. Is it true that the cohort 21 studies that you discuss in those pages of 22 your report do not include specific dose 23 information? 24 A. We'd have to look at each</p>	<p style="text-align: right;">Page 413</p> <p>1 dose-response to you? 2 MR. FROST: Objection. 3 A. Again, it mentions duration of 4 exposure, which is one component of dose. 5 BY MR. SOILEAU: 6 Q. Well, it says more than 7 duration of exposure. It says became more 8 extensive and severe with duration of 9 exposure. Here, you can have my page for a 10 moment. 11 More severe, more extensive 12 with duration. Isn't that dose-response? 13 MR. FROST: Objection. 14 A. Well, again, as I said, 15 duration is one component of dose, so -- 16 BY MR. SOILEAU: 17 Q. Right. 18 A. -- that's certainly 19 preliminary, but again -- 20 Q. So doesn't that say -- 21 A. -- we need to look at that -- 22 that is one sentence. I'd need to look at 23 the data supporting it, but duration is 24 definitely a component of dose.</p>

104 (Pages 410 to 413)

Kelly Tuttle, Ph.D.

Page 414	Page 416
<p>1 Q. Right. But when we have 2 increased dose and increased biological 3 effects, that is, when the effects, the 4 adverse biological effects increase when the 5 dose increases, isn't that the essence of 6 dose-response? 7 A. That is the study of 8 dose-response, whether the symptom or 9 potential adverse health effect is associated 10 with the dose of a product. 11 Q. Right. And NTP in that 12 sentence is describing something that is 13 dose-responsive? 14 MR. FROST: Objection. 15 BY MR. SOILEAU: 16 Q. An adverse biological effect 17 that is dose-responsive? 18 MR. FROST: Objection. 19 A. Again, in that particular 20 sentence where they're looking at the 21 hyperplasias from inhalational exposure, they 22 certainly note that the hyperplasias were 23 associated with duration. 24 ///</p>	<p>1 Q. Okay. Didn't the authors in 2 the study marked now as Tuttle Exhibit 37 3 note a dose-response relationship with the 4 duration of use and number of lifetime 5 applications? 6 A. Yes, I believe I state that in 7 my report, that the authors noted a 8 dose-response based on duration and number of 9 lifetime applications. 10 If I may, I'm sorry. 11 Q. Go ahead. Have at it. 12 A. I was just looking at my report 13 on page 25, where I also note that the 14 significance disappeared when they were 15 interviewed prior or after 2014, and I'm 16 looking for the table in the actual report as 17 well. 18 Q. Okay. Was this study adjusted 19 for litigation-based bias? 20 MR. FROST: Objection. 21 A. Again -- 22 BY MR. SOILEAU: 23 Q. Is that what you're talking 24 about?</p>
Page 415	Page 417
<p>1 BY MR. SOILEAU: 2 Q. Did the Schildkraut study that 3 you looked at in your report include a 4 dose-response relationship? 5 A. I would need to -- 6 Q. You need it. I'll give you a 7 copy marked as Tuttle Exhibit 37. 8 (Whereupon, Deposition Exhibit 9 Tuttle-37, 2016 Schildkraut et al 10 Publication, was marked for 11 identification.) 12 BY MR. SOILEAU: 13 Q. This is a study that you 14 reference in your discussion of epidemiology, 15 isn't it? 16 A. Yes, I believe so. I'm 17 actually looking for the spot where I 18 reference it in my report. 19 Q. Okay. Do you want to look in 20 your reference list to confirm that you cite 21 it? 22 A. Certainly. Yes. 23 Q. Look at page 25. 24 A. Yes.</p>	<p>1 A. You know, they noted that there 2 was a difference between pre and post 2014, 3 and I believe that they state something about 4 the media, and I think I quoted heightened 5 awareness of the exposure as a result of two 6 recent class action lawsuits. 7 Q. But my question, Doctor, is: 8 Did the authors of this study adjust for that 9 effect? 10 A. As I said, they examined the 11 individuals that were interviewed by whether 12 they were interviewed prior to 2014 or after 13 2014. 14 Q. Did you state that the 15 case-control studies were not consistent in 16 your report? 17 A. I believe that I stated that 18 the scientific evidence -- and I actually can 19 refer to the summary in my report so I can 20 make sure I'm accurate regarding the 21 consistency. 22 I believe I say there is little 23 to no consistency among the scientific 24 literature between the studies as shown by</p>

105 (Pages 414 to 417)

Kelly Tuttle, Ph.D.

<p style="text-align: right;">Page 418</p> <p>1 the variation between population and</p> <p>2 hospital-based studies and between</p> <p>3 case-control and cohort studies, mode of</p> <p>4 genetic talc application and other places,</p> <p>5 circumstances and times.</p> <p>6 Q. What was your conclusion about</p> <p>7 the -- well, you reviewed the case-control</p> <p>8 studies in your report, right? You list them</p> <p>9 and discuss them briefly?</p> <p>10 A. Yes, that's correct.</p> <p>11 Q. And what was the conclusion</p> <p>12 that you reached? I don't know that I saw</p> <p>13 that you said based on these studies I</p> <p>14 conclude that the case-control studies offer</p> <p>15 some evidence, no evidence or otherwise</p> <p>16 describe what evidence those offer.</p> <p>17 Do you understand what I'm</p> <p>18 saying?</p> <p>19 A. Yes, I think I do. And if you</p> <p>20 refer --</p> <p>21 Q. Did I miss it?</p> <p>22 A. If you refer to page --</p> <p>23 MR. FROST: Objection.</p> <p>24 MR. SOILEAU: Sorry.</p>	<p style="text-align: right;">Page 420</p> <p>1 office. As I said previously, I'm based out</p> <p>2 of my home right now.</p> <p>3 Q. Have you seen this article</p> <p>4 before today?</p> <p>5 A. Yes, I believe I have.</p> <p>6 Q. And in what circumstances did</p> <p>7 you come to see this article?</p> <p>8 A. I guess I'm trying to think</p> <p>9 specifically. I'm not entirely sure. As I</p> <p>10 said, I think have a passing familiarity. I</p> <p>11 think I remember seeing something about it</p> <p>12 generally in the Nature journal.</p> <p>13 Q. Do you see the subheading on</p> <p>14 the first page, Pervasive Problem?</p> <p>15 A. Yes, I do.</p> <p>16 Q. It says in that paragraph:</p> <p>17 Let's be clear about what must stop: We</p> <p>18 should never conclude there is no difference</p> <p>19 or no association just because a p value is</p> <p>20 larger than a threshold such as 0.05 or,</p> <p>21 equivalently, because a confidence interval</p> <p>22 includes zero. Neither should we conclude</p> <p>23 that two studies conflict because one had a</p> <p>24 statistically significant result and the</p>
<p style="text-align: right;">Page 419</p> <p>1 A. If you refer to page 29 of my</p> <p>2 report, after the summary of the various</p> <p>3 scientific literature regarding, you know,</p> <p>4 the epidemiological studies, there's a</p> <p>5 section called Conclusion and Bradford Hill</p> <p>6 Criteria.</p> <p>7 BY MR. SOILEAU:</p> <p>8 Q. Let me show you something I've</p> <p>9 marked as Tuttle Exhibit 38.</p> <p>10 (Whereupon, Deposition Exhibit</p> <p>11 Tuttle-38, Article, Retire Statistical</p> <p>12 Significance, was marked for</p> <p>13 identification.)</p> <p>14 BY MR. SOILEAU:</p> <p>15 Q. Have you had a chance to see</p> <p>16 this comment that was recently published in</p> <p>17 Nature? Do you recognize that journal,</p> <p>18 Nature?</p> <p>19 A. Yes, I know the journal Nature.</p> <p>20 Q. Very good.</p> <p>21 Do you receive it or does CTEH</p> <p>22 receive it?</p> <p>23 A. I don't receive it. I'm not</p> <p>24 sure if CTEH receives it at the corporate</p>	<p style="text-align: right;">Page 421</p> <p>1 other did not. These errors waste research</p> <p>2 efforts and misinform policy decisions. We</p> <p>3 agree, and call for the entire concept of</p> <p>4 statistical significance to be abandoned.</p> <p>5 That ends the quote.</p> <p>6 Are you in a position to agree</p> <p>7 or disagree with that statement?</p> <p>8 MR. FROST: Objection.</p> <p>9 A. I'm sorry, you jumped from that</p> <p>10 paragraph to -- to the next -- when you were</p> <p>11 reading that, so I don't know where you --</p> <p>12 your last sentence came from.</p> <p>13 BY MR. SOILEAU:</p> <p>14 Q. Oh, I went to the second page.</p> <p>15 I'm sorry. I turned the page.</p> <p>16 A. No, I mean, when you ended that</p> <p>17 paragraph, the paragraph ends with "these</p> <p>18 errors," and then the next paragraph says,</p> <p>19 "For example," so I don't know where you went</p> <p>20 to get the --</p> <p>21 MR. FROST: Yeah, the "we</p> <p>22 agree" part.</p> <p>23 A. -- last sentence.</p> <p>24 MR. FROST: I don't know where</p>

Kelly Tuttle, Ph.D.

Page 422	Page 424
<p>1 that's coming from.</p> <p>2 MR. SOILEAU: Oh, okay. I'm</p> <p>3 sorry.</p> <p>4 BY MR. SOILEAU:</p> <p>5 Q. "These errors waste research</p> <p>6 efforts and misinform policy decisions." I</p> <p>7 don't know, so I'm sorry.</p> <p>8 Would you like me to read it</p> <p>9 again?</p> <p>10 A. Please.</p> <p>11 Q. It says: Let's be clear about</p> <p>12 what must stop: We should never conclude</p> <p>13 there is no difference or no association just</p> <p>14 because a p value is larger than a threshold</p> <p>15 such as 0.05 or, equivalently, because a</p> <p>16 confidence interval includes zero. Neither</p> <p>17 should we conclude that the two studies</p> <p>18 conflict because one had a statistically</p> <p>19 significant result and the other did not.</p> <p>20 These efforts waste research efforts and</p> <p>21 misinform policy decisions.</p> <p>22 Are you in a position to agree</p> <p>23 or disagree with that?</p> <p>24 MR. FROST: Objection.</p>	<p>1 the talcum powder products be transported</p> <p>2 within the lattice of the talc?</p> <p>3 A. I think we're getting out of</p> <p>4 the realm of what I assess in regards to</p> <p>5 heavy metals in my report. As I previously</p> <p>6 said, any of the research around talcum</p> <p>7 powder and talcum powder products, if we</p> <p>8 assume heavy metals are present, then that</p> <p>9 scientific evidence would include any</p> <p>10 products that would be in the talcum powder.</p> <p>11 Q. But if the heavy metal is</p> <p>12 present, it's present in the talcum powder,</p> <p>13 right?</p> <p>14 A. That's what I said. If we, you</p> <p>15 know, assume that the heavy metals are</p> <p>16 present in the talcum powder, then any</p> <p>17 testing or any of the epidemiological studies</p> <p>18 that look at talcum powder would include</p> <p>19 heavy metals or other -- anything that was</p> <p>20 present in the talcum powder.</p> <p>21 Q. Okay. Because the effect, any</p> <p>22 adverse biological effect presented by the</p> <p>23 heavy metals would be combined with whatever</p> <p>24 else is going on with the talcum powder</p>
Page 423	Page 425
<p>1 A. Well, as we said previously on</p> <p>2 other things, this is -- this is one</p> <p>3 paragraph taken out of a three-page --</p> <p>4 appears to be an opinion piece or a comment</p> <p>5 piece as listed at the beginning of the</p> <p>6 document, so I don't see any scientific data</p> <p>7 or anything like that.</p> <p>8 It appears to be an opinion, so</p> <p>9 as such, I can't -- I mean, I can't agree or</p> <p>10 disagree.</p> <p>11 BY MR. SOILEAU:</p> <p>12 Q. Do you have any idea how many</p> <p>13 epidemiologists or biostatisticians signed on</p> <p>14 to this opinion piece?</p> <p>15 A. I see three authors, and then I</p> <p>16 see something about 800 signatories. But I</p> <p>17 have no clue the qualifications or any of</p> <p>18 that of who the signatories are.</p> <p>19 Q. Or the authors for that matter?</p> <p>20 A. That's correct.</p> <p>21 Q. I want to ask you a couple of</p> <p>22 questions about heavy metals. You talk about</p> <p>23 heavy metals in your report. In your</p> <p>24 opinion, will any heavy metals included in</p>	<p>1 products, fair?</p> <p>2 A. As I said, any study that would</p> <p>3 look at the talcum powder products would</p> <p>4 include anything that was present in the</p> <p>5 talcum powder.</p> <p>6 Q. But does the talc have the</p> <p>7 ability to transport within the lattice of</p> <p>8 the talc heavy metals?</p> <p>9 MR. FROST: Objection.</p> <p>10 BY MR. SOILEAU:</p> <p>11 Q. Do you know what I mean by</p> <p>12 lattice?</p> <p>13 A. I -- I was about to just answer</p> <p>14 that I don't know.</p> <p>15 Q. Okay. Do you maintain that the</p> <p>16 use of background limits for ambient air is</p> <p>17 appropriate when we're concerned about</p> <p>18 ovarian tissue?</p> <p>19 MR. FROST: Objection.</p> <p>20 A. Can you --</p> <p>21 MR. FROST: As to what? Yeah.</p> <p>22 BY MR. SOILEAU:</p> <p>23 Q. Well, in your report you talk</p> <p>24 ambient air, correct? Background levels of</p>

107 (Pages 422 to 425)

Kelly Tuttle, Ph.D.

<p style="text-align: right;">Page 426</p> <p>1 exposure based on ambient air and standards</p> <p>2 that apply to ambient air; is that right?</p> <p>3 A. I believe I discuss ambient air</p> <p>4 in regards to background levels of exposure</p> <p>5 to asbestos.</p> <p>6 Q. And you believe that's an</p> <p>7 appropriate methodology, that is, that you</p> <p>8 can use those ambient air standards in the</p> <p>9 instance of ovarian cancer issues?</p> <p>10 A. Well, I'm not aware of ambient</p> <p>11 air standards. I refer to the fact that</p> <p>12 everybody is exposed to background levels of</p> <p>13 asbestos in a brief discussion regarding the</p> <p>14 available information regarding airborne</p> <p>15 exposures to asbestos as related to talcum</p> <p>16 powder use, but for the -- again, for the</p> <p>17 majority of my report, I'm referencing the</p> <p>18 perineal application and --</p> <p>19 Q. Do you disagree or agree that</p> <p>20 there is no safe level of asbestos to talcum</p> <p>21 powder products?</p> <p>22 MR. FROST: Objection.</p> <p>23 A. I'm sorry, can you repeat that</p> <p>24 one more time for me?</p>	<p style="text-align: right;">Page 428</p> <p>1 day, each diapering?</p> <p>2 A. Not necessarily each diapering,</p> <p>3 but I believe I use it every day.</p> <p>4 Q. Are you aware of the corn</p> <p>5 starch alternative?</p> <p>6 MR. FROST: Objection.</p> <p>7 A. I'm aware that some powder</p> <p>8 products use cornstarch as opposed to talc,</p> <p>9 yes.</p> <p>10 BY MR. SOILEAU:</p> <p>11 Q. Did you make a decision to use</p> <p>12 the talc products instead of the cornstarch</p> <p>13 products?</p> <p>14 A. I don't believe that I made a</p> <p>15 conscious decision one way or the other. I</p> <p>16 bought Johnson &amp; Johnson baby powder for use</p> <p>17 on my child, and in the course of curiosity</p> <p>18 as moving forward with this, I did check the</p> <p>19 ingredients, and it is the talc-containing</p> <p>20 one.</p> <p>21 Q. But you understand there's a</p> <p>22 choice between talcum powder products in the</p> <p>23 baby powder line and cornstarch products?</p> <p>24 MR. FROST: Objection.</p>
<p style="text-align: right;">Page 427</p> <p>1 BY MR. SOILEAU:</p> <p>2 Q. I only want you to answer if</p> <p>3 you can tell me you agree or disagree,</p> <p>4 because we -- we're out of time almost.</p> <p>5 Is there any safe level or can</p> <p>6 you agree there is no safe level of asbestos</p> <p>7 when it comes to talcum powder products?</p> <p>8 MR. FROST: Objection.</p> <p>9 BY MR. SOILEAU:</p> <p>10 Q. Are you able to agree or</p> <p>11 disagree with that?</p> <p>12 A. I can't agree or disagree</p> <p>13 without more discussion.</p> <p>14 Q. Okay. I'm going to have to ask</p> <p>15 you. You said that you made an election to</p> <p>16 use Johnson baby powder on your newborn.</p> <p>17 Do you use it daily on him?</p> <p>18 MR. FROST: Objection, outside</p> <p>19 of the scope of the expert opinions</p> <p>20 being offered here.</p> <p>21 MR. SOILEAU: Well, I disagree.</p> <p>22 MR. FROST: You can answer.</p> <p>23 BY MR. SOILEAU:</p> <p>24 Q. I mean, do you use it every</p>	<p style="text-align: right;">Page 429</p> <p>1 A. I was not specifically aware of</p> <p>2 that, no.</p> <p>3 BY MR. SOILEAU:</p> <p>4 Q. Do you know which one you're</p> <p>5 buying?</p> <p>6 MR. FROST: Objection, asked</p> <p>7 and answered.</p> <p>8 A. As I just said, I ended up</p> <p>9 looking at the bottle after purchasing it and</p> <p>10 saw that it is the talc-containing one.</p> <p>11 BY MR. SOILEAU:</p> <p>12 Q. Do you intend to continue to</p> <p>13 use that product, the talcum powder product,</p> <p>14 for your newborn?</p> <p>15 A. Yes, I do.</p> <p>16 Q. Have you read the warning on</p> <p>17 the bottle?</p> <p>18 A. Goodness.</p> <p>19 MR. FROST: Objection.</p> <p>20 A. I'm trying to remember. I'm</p> <p>21 sure I probably saw it, but I can't remember</p> <p>22 what it said off the top of my head.</p> <p>23 BY MR. SOILEAU:</p> <p>24 Q. Do you know anything about the</p>

108 (Pages 426 to 429)



Kelly Tuttle, Ph.D.

<p style="text-align: right;">Page 430</p> <p>1 proper use of Johnson's baby powder for an 2 infant? 3 MR. FROST: Objection. 4 A. I know how I use it. I don't 5 know what you mean by proper use. 6 BY MR. SOILEAU: 7 Q. Do you know if there's a 8 warning about inhalation hazards for 9 Johnson's -- Johnson &amp; Johnson's talcum 10 powder baby powder? 11 MR. FROST: Objection. 12 A. Again, I remember there being 13 a -- I think there was a warning. I don't 14 remember specifics about what it said. 15 BY MR. SOILEAU: 16 Q. Are you aware of any talcum 17 powder products that carry a warning 18 regarding a risk of ovarian cancer? 19 MR. FROST: Objection. 20 A. No, I'm not aware of that. 21 MR. FROST: How are we doing on 22 time? We're done? 23 MR. SOILEAU: Okay. I'm going 24 to have to note just for the purposes</p>	<p style="text-align: right;">Page 432</p> <p>1 CERTIFICATE 2 I, SUSAN PERRY MILLER, Registered 3 Diplomate Reporter, Certified Realtime 4 Reporter, Certified Court Reporter and Notary 5 Public, do hereby certify that prior to the 6 commencement of the examination, KELLY 7 TUTTLE, Ph.D., was duly sworn by me to 8 testify to the truth, the whole truth and 9 nothing but the truth. 10 11 I DO FURTHER CERTIFY that the 12 foregoing is a verbatim transcript of the 13 testimony as taken stenographically by and 14 before me at the time, place and on the date 15 hereinbefore set forth, to the best of my 16 ability. 17 I DO FURTHER CERTIFY that pursuant 18 to FRCP Rule 30, signature of the witness was 19 not requested by the witness or other party 20 before the conclusion of the deposition. 21 22 I DO FURTHER CERTIFY that I am 23 neither a relative nor employee nor attorney 24 nor counsel of any of the parties to this action, and that I am neither a relative nor employee of such attorney or counsel, and that I am not financially interested in the action.  SUSAN PERRY MILLER, RDR, CRR Fellow of the Academy of Professional Reporters NCRA Registered Diplomate Reporter NCRA Certified Realtime Reporter Certified Court Reporter Notary Public in and for the State of Texas My Commission Expires: 7/9/2020 Dated: April 12, 2019</p>
<p style="text-align: right;">Page 431</p> <p>1 of the record, we've had a lot of 2 long, nonresponsive answers, so I 3 think we will reserve our right to 4 consider a request for more time if 5 necessary just because of the 6 nonresponsiveness and length of some 7 of the answers. 8 MR. FROST: Okay. Obviously -- 9 MR. SOILEAU: I know that's 10 something we don't agree on. 11 MR. FROST: I was going to say, 12 we disagree on that, but that's fine. 13 You can note it for the record. 14 MR. SOILEAU: That's fine. All 15 right. I think that concludes the 16 deposition. 17 MR. FROST: Yeah, I don't have 18 any questions. 19 THE VIDEOGRAPHER: This marks 20 the end of the deposition. We're 21 going off the record at 6:16 p.m. 22 (Proceedings recessed at 23 6:16 p.m.) 24 --o0o--</p>	<p style="text-align: right;">Page 433</p> <p>1 INSTRUCTIONS TO WITNESS 2 3 Please read your deposition over 4 carefully and make any necessary corrections. 5 You should state the reason in the 6 appropriate space on the errata sheet for any 7 corrections that are made. 8 After doing so, please sign the 9 errata sheet and date it. 10 You are signing same subject to 11 the changes you have noted on the errata 12 sheet, which will be attached to your 13 deposition. 14 It is imperative that you return 15 the original errata sheet to the deposing 16 attorney within thirty (30) days of receipt 17 of the deposition transcript by you. If you 18 fail to do so, the deposition transcript may 19 be deemed to be accurate and may be used in 20 court. 21 22 23 24</p>

109 (Pages 430 to 433)

Kelly Tuttle, Ph.D.

<p style="text-align: right; margin-right: 50px;">Page 434</p> <div style="display: flex; justify-content: space-between;"> <div style="width: 10%;"> <p>1</p><p>2</p><p>3</p><p>4</p><p>5</p><p>6</p><p>7</p><p>8</p><p>9</p><p>10</p><p>11</p><p>12</p><p>13</p><p>14</p><p>15</p><p>16</p><p>17</p><p>18</p><p>19</p><p>20</p><p>21</p><p>22</p><p>23</p><p>24</p> </div> <div style="width: 85%;"> <p style="text-align: center;">ERRATA</p> <p>PAGE LINE CHANGE</p> <p>REASON: _____</p> <p>REASON: _____</p> <p>REASON: _____</p> <p>REASON: _____</p> <p>REASON: _____</p> <p>REASON: _____</p> <p>REASON: _____</p> <p>REASON: _____</p> <p>REASON: _____</p> <p>REASON: _____</p> <p>REASON: _____</p> <p>REASON: _____</p> <p>REASON: _____</p> <p>REASON: _____</p> </div> </div>	<p style="text-align: right; margin-right: 50px;">Page 436</p> <div style="display: flex; justify-content: space-between;"> <div style="width: 10%;"> <p>1</p><p>2</p><p>3</p><p>4</p><p>5</p><p>6</p><p>7</p><p>8</p><p>9</p><p>10</p><p>11</p><p>12</p><p>13</p><p>14</p><p>15</p><p>16</p><p>17</p><p>18</p><p>19</p><p>20</p><p>21</p><p>22</p><p>23</p><p>24</p> </div> <div style="width: 85%;"> <p style="text-align: center;">LAWYER'S NOTES</p> <p>PAGE LINE</p> <p>_____</p> <p>_____</p> <p>_____</p> <p>_____</p> <p>_____</p> <p>_____</p> <p>_____</p> <p>_____</p> <p>_____</p> <p>_____</p> <p>_____</p> <p>_____</p> <p>_____</p> <p>_____</p> </div> </div>
<p style="text-align: right; margin-right: 50px;">Page 435</p> <div style="display: flex; justify-content: space-between;"> <div style="width: 10%;"> <p>1</p><p>2</p><p>3</p><p>4</p><p>5</p><p>6</p><p>7</p><p>8</p><p>9</p><p>10</p><p>11</p><p>12</p><p>13</p><p>14</p><p>15</p><p>16</p><p>17</p><p>18</p><p>19</p><p>20</p><p>21</p><p>22</p><p>23</p><p>24</p> </div> <div style="width: 85%;"> <p style="text-align: center;">ACKNOWLEDGMENT OF DEPONENT</p> <p>I, KELLY TUTTLE, Ph.D., do hereby certify that I have read the foregoing pages and that the same is a correct transcription of the answers given by me to the questions therein propounded, except for the corrections or changes in form or substance, if any, noted in the attached Errata Sheet.</p> <p>_____</p> <p>KELLY TUTTLE, Ph.D.                      DATE</p> <p>Subscribed and sworn to before me this _____ day of _____, 20 ____.</p> <p>My commission expires: _____</p> <p>_____</p> <p>Notary Public</p> </div> </div>	

<b>A</b>	<b>accurate</b> 115:7	315:20 391:14	235:18 239:21	370:6,20 371:2
<b>a.m</b> 1:17 8:2,7	116:23 220:10	391:16 393:2	<b>agency</b> 141:21	388:22 390:8
86:9,10,11,13	411:11 417:20	<b>addressed</b> 32:7	151:8 200:12	395:10 406:8
147:15,16	433:19	132:18 143:16	200:20 201:7	421:3,6,22
<b>A.O</b> 13:2	<b>accurately</b>	281:18 293:11	235:11 238:8	422:22 423:9
<b>A.P</b> 249:4	157:14 322:24	320:8	238:16 239:24	426:19 427:3,6
250:18 251:2,9	324:11 344:8	<b>addresses</b> 207:7	277:8	427:10,12
251:19 293:3	<b>acid</b> 289:22	390:23	<b>agent</b> 13:15	431:10
<b>abandoned</b>	<b>acknowledge</b>	<b>addressing</b>	14:14 25:1	<b>agree/disagree</b>
421:4	124:21 136:4	11:14 62:12	159:13 218:15	84:22
<b>ability</b> 49:24	359:10	185:23 192:6	222:21 317:6	<b>agreed</b> 343:18
138:2,24 140:5	<b>ACKNOWLEDGE...</b>	231:10 232:23	344:4	352:15 356:14
191:8 333:23	4:11 435:1	238:23 283:13	<b>agents</b> 17:11	<b>agreement</b>
425:7 432:9	<b>acronym</b> 223:2	283:14	18:20 19:19	181:5
<b>able</b> 22:23 51:11	262:1,6	<b>addressings</b>	23:15 24:2	<b>aha</b> 70:10
60:7,18 74:18	<b>action</b> 417:6	137:24	343:20	<b>ahead</b> 26:6 55:2
84:20 130:6	432:14,15	<b>adjust</b> 417:8	<b>ago</b> 8:24 12:2	79:21 84:24
131:24 156:3	<b>activate</b> 323:23	<b>adjusted</b> 416:18	37:15,16 42:20	86:5 94:22
157:13 178:14	<b>activated</b> 321:20	<b>Administration</b>	65:9 80:10	103:20 114:19
178:21 180:16	<b>actual</b> 16:18	225:3,7,11,13	135:9 329:16	130:13 143:3
184:16 195:18	75:1 165:22	226:4 354:19	392:12 410:9	158:2 197:24
196:9 218:24	287:1 289:5	<b>administrative</b>	<b>agree</b> 17:9 18:23	219:19 237:1
283:19 286:1	349:3 354:9	100:8,23	19:12 22:15,22	238:17 258:18
313:15 324:20	411:14 416:16	<b>admittedly</b> 36:5	22:23 23:5,9	311:19 320:3
340:20 350:7	<b>acute</b> 311:6	<b>adopted</b> 229:23	23:19 24:4,16	349:14 351:9
368:8 405:2	313:6 317:19	<b>adverse</b> 17:10	51:5,13 52:2	363:23 372:15
412:2 427:10	<b>add</b> 163:1 165:9	17:15 18:19	55:14,23 64:21	416:11
<b>absence</b> 244:22	<b>added</b> 202:7	19:3,8,18	83:15 84:14	<b>aimed</b> 34:22
342:15	203:4 293:19	23:14,17 24:1	88:18 104:16	<b>air</b> 425:16,24
<b>absent</b> 154:8	<b>addition</b> 19:16	24:6,15,18	107:23 122:20	426:1,2,3,8,11
<b>Absolutely</b>	97:10,23	25:2,7 91:22	168:18,24	<b>airborne</b> 426:14
83:23 224:23	<b>additional</b> 17:22	92:7 130:8	178:24 180:2	<b>airways</b> 312:16
<b>abstract</b> 170:21	26:12 49:19	138:19 139:18	183:24 188:13	321:8
<b>Academy</b>	51:9 96:20	210:12 241:1	229:11 230:21	<b>al</b> 5:20,22 6:2,4
262:11,15,18	144:9 148:7	242:1 243:1	231:3,18	6:5,7,20 7:10
432:18	159:16 174:12	305:18,19	232:11,16	159:19 164:12
<b>accept</b> 75:23	261:5 275:2,16	343:19,23	234:6 272:9,24	166:15 170:13
169:24	291:4 318:16	408:5 414:4,9	273:22 274:12	172:8 174:16
<b>accepted</b> 20:21	<b>address</b> 52:20	414:16 424:22	274:13,24	190:6 202:24
59:21 80:21	64:12 89:7	<b>advised</b> 223:23	275:14 276:19	206:13 207:3
178:19	123:11 127:11	<b>afraid</b> 311:12	277:1 278:7,14	320:17 415:9
<b>access</b> 105:4	129:6 133:16	405:5	305:21 306:7	<b>Alabama</b> 2:10
<b>accomplished</b>	140:11,17	<b>afternoon</b>	306:13 307:13	<b>Alexandria</b> 2:15
108:6	141:2 179:1	147:21 194:3	309:19 310:17	<b>Alfred</b> 262:10
<b>account</b> 356:19	185:23 236:19	303:5	325:4 356:11	278:19 279:4
<b>accuracy</b> 78:4	252:13 281:11	<b>agencies</b> 58:13	361:11,16	293:15
	292:2 315:16	201:1 208:6	363:17 369:19	<b>allegation</b> 14:18

<b>ALLEN</b> 2:8	387:1,8,9,12	<b>anticipated</b>	<b>application</b>	<b>applications</b>
<b>allow</b> 89:2,9,23	387:17 388:5	342:10	62:21 65:20	416:5,9
165:24	389:19 390:24	<b>anus</b> 199:14	68:8 88:15,19	<b>applied</b> 25:5
<b>allows</b> 236:4	391:1,18,20	<b>apologize</b> 58:16	89:1,8,22 91:2	27:1 45:18
277:1	393:11 394:10	94:21 161:21	91:5 107:15	57:14 110:4
<b>alphabetized</b>	396:2,3,3,9,10	201:13 262:7	108:15 109:7	116:8 136:24
158:4	396:15,19,24	385:22	110:10,14,19	139:14 175:7
<b>alternative</b>	396:24 397:3,7	<b>apparent</b> 38:3	110:24 111:3,8	175:23 176:21
213:5,11	397:15,21	<b>apparently</b>	111:16 112:7	213:14,20
286:14 428:5	398:4 405:18	173:22 219:7	112:14 113:20	215:11 244:18
<b>alveolar</b> 321:9	406:17 408:1,5	264:5	114:8 115:11	260:2 333:24
321:22,23	408:12,24	<b>appear</b> 44:8	115:14 116:7	340:22 348:16
322:9,10	409:21 410:2	165:3 252:18	119:9 120:10	403:17 410:3
402:23 403:15	410:13	353:21	123:8 124:15	<b>applies</b> 408:16
404:8	<b>animals</b> 17:16	<b>APPEARAN...</b>	126:8 127:19	409:3
<b>ambient</b> 425:16	19:20 130:9	4:2	130:22 135:18	<b>apply</b> 28:13,15
425:24 426:1,2	150:1 396:11	<b>appearing</b> 9:1	136:12 150:16	87:11 267:1
426:3,8,10	397:18 406:20	<b>appears</b> 11:7	152:4,5 159:6	268:4 272:3
<b>amelioration</b>	408:14 409:2	23:2 147:9	165:15 166:23	396:4,20 397:4
23:17	410:17	161:9 163:3	166:24 169:7	409:23,24
<b>amount</b> 64:15	<b>annoyed</b> 201:10	171:5,6 173:11	169:16 171:12	426:2
393:10 394:9	<b>answer</b> 19:12	198:11,23	176:1 177:8	<b>applying</b> 123:1
<b>AMs</b> 321:15,17	27:13 28:1,16	199:23 202:3	178:9 179:1,3	267:8 268:1
322:14	52:12 60:18	218:19 219:11	179:15,24	270:19 271:10
<b>analyses</b> 393:14	65:5 84:21,23	281:16 423:4,8	180:19 184:12	<b>appreciate</b>
<b>analysis</b> 119:12	107:6 118:11	<b>appendices</b>	184:19 189:23	117:1 124:7
137:9 216:16	118:12 122:15	10:14 11:1,8	192:7 194:10	130:11 156:12
241:8 244:4	125:4 236:24	12:1 216:22	195:7,12,23	341:11 356:1
246:12 285:13	241:21 246:9	217:7	206:16 208:19	<b>approach</b> 29:6
288:11,15	257:20,22	<b>appendix</b> 6:18	209:10,23	77:14
295:17 297:22	258:8,15 267:9	12:12 284:12	211:13 212:23	<b>appropriate</b>
298:4,5 304:8	268:23 311:20	284:15,20,24	214:3,18 216:6	15:24 51:2
382:2	320:4 360:6	285:19 286:2,4	229:16 230:10	54:11 55:24
<b>analyzed</b> 288:9	373:12 375:3	286:19,22	232:2,4 233:9	56:18 59:7
<b>analyzing</b>	398:6 425:13	287:11 288:3	233:20,22	127:19 128:11
296:10	427:2,22	289:13 366:13	241:15 242:12	129:19 299:19
<b>anatomy</b> 130:3	<b>answered</b>	367:5,15,18	242:17 245:13	397:22 398:9
132:11 397:18	360:18,22	368:1 373:20	246:18 248:23	425:17 426:7
397:19 406:20	373:10 429:7	379:19	250:11 260:16	433:6
410:17,21,24	<b>answering</b> 10:8	<b>apple</b> 239:13	267:14 268:12	<b>appropriately</b>
<b>ANDERTON</b>	198:20 339:9	<b>apples</b> 239:10	269:1 303:16	58:19 60:19
3:7	377:22	239:12	304:17,18	122:15
<b>Angeles</b> 2:21	<b>answers</b> 361:15	<b>applicable</b> 64:17	305:4 332:13	<b>approximately</b>
<b>angle</b> 29:7	388:20 394:1	65:3 180:18	333:4,10,17	276:13
209:20	431:2,7 435:5	214:22 351:22	345:3 397:16	<b>April</b> 1:12 5:2
<b>animal</b> 383:2,9	<b>anthophyllite</b>	408:15 409:3	403:19 418:4	8:2,6 218:3
383:13 386:19	161:12	409:20	426:18	219:23 225:4

432:23	239:20 252:18	377:13,16,24	234:21 241:8	270:19 275:20
<b>area</b> 34:3 48:18	254:12,16,16	378:6,14 379:1	241:20 242:9	303:3 356:20
49:12 89:3,10	254:19,21,22	379:7,8,16,21	242:10 243:24	365:6 367:1
89:23 108:6	255:5,8,15,19	380:7,13,17	264:8 273:21	381:15 382:16
111:9,17	256:19 258:21	381:12,18	274:3 299:16	<b>assessment</b> 6:10
112:16 113:21	277:15 320:13	382:11 426:5	310:3 311:16	7:3 16:12
114:9 116:8	320:22 321:1	426:13,15,20	329:11 331:18	40:20 43:16
138:5 167:10	325:21 326:1	427:6	335:20 343:2	57:17 58:2,14
186:1 199:13	328:20 329:1	<b>asbestos-cont...</b>	345:8 348:11	58:20 59:8,13
250:12 252:19	329:12 342:23	352:5 353:20	356:2 358:22	59:16,19,24
260:2 295:20	384:11 395:9	353:24 357:24	358:24 359:3,9	60:3,14,16,22
296:12,13	400:16 419:11	359:1,23 362:2	359:16 360:13	60:23 63:1
297:7 315:12	420:3,7	371:13 381:1	370:1,3 374:24	91:1 104:24
329:20 339:7	<b>articles</b> 35:14	<b>ASHCRAFT</b>	391:24 392:2	105:9,16,22
339:23 365:18	37:17 40:10	2:13	397:9	129:8 193:15
383:10 385:13	42:17 64:10	<b>Ashton</b> 219:9	<b>aspect</b> 126:4	201:18,24
388:8	169:3 177:3,6	222:10 327:22	<b>aspects</b> 49:16,17	211:5 214:21
<b>areas</b> 227:5	188:5,6 191:1	<b>aside</b> 191:13	72:3 394:16	215:20 222:6
298:14 400:11	192:1 195:18	194:11	<b>aspire</b> 64:23	283:2 301:1
402:2	205:12 206:4	<b>asked</b> 10:9	<b>assembled</b> 123:6	314:23 324:18
<b>argument</b>	253:20,22	11:11,17 14:22	<b>assert</b> 396:16	330:12 335:2
127:23 137:22	255:21 256:3	16:5 24:16	<b>assess</b> 27:18	344:24 345:13
<b>arguments</b>	258:24 277:8	25:4 27:17	29:9 30:7 49:3	346:12 347:4,7
128:5	302:20 304:13	35:4 38:5	56:7 57:10	347:15 348:2,6
<b>Arkansas</b> 18:9	328:8 358:18	54:10 57:10	62:17 112:10	348:14 349:4,8
384:20 385:2,9	401:2	62:3,4,17	148:22 149:9	349:17 356:20
385:17	<b>asbestos</b> 7:6	66:20 67:9	208:19,23	393:14
<b>arose</b> 22:9	13:16,21 14:4	174:10 212:5	213:9 241:14	<b>assessments</b>
<b>arrive</b> 28:16	14:20 161:12	212:16 236:8	287:15 292:5	16:11 52:13
107:16 123:2	162:21 312:5	248:19 298:7	297:22 298:15	58:6,9
267:9	353:20 355:5	325:18 360:7	367:9 368:7,24	<b>assimilate</b> 63:6
<b>art</b> 121:20	355:12,13,15	360:17,22	390:16 394:13	<b>assist</b> 54:10
<b>Arthur</b> 203:8	355:19 356:3,4	361:13 373:9	424:4	<b>assistant</b> 341:19
<b>article</b> 7:12	356:23 362:13	376:5,8 378:22	<b>assessed</b> 16:21	<b>assisted</b> 100:2
65:14 70:23	363:4,15	394:12 397:2	31:23 113:11	287:1
72:19 74:14	366:13,17,21	429:6	113:17 119:19	<b>assisting</b> 98:9
75:1 85:4,6	367:1,4,20,24	<b>asking</b> 23:1,3	212:21 233:8	<b>associated</b> 30:12
113:15 159:3	368:4,22	47:3 48:1,21	245:5 265:18	51:4,21 52:4
163:3 165:12	369:13,23	52:23 53:1	266:3 271:1	54:11 57:6
169:2 170:10	370:6,12,21	55:3,6 60:11	290:12 343:11	66:24 198:10
171:17,22	371:4,20 373:1	60:13 103:12	<b>assessing</b> 24:24	242:13 336:13
172:24 173:22	373:4,7,19,21	108:22 160:18	27:10 28:6,21	355:20,24
176:6 178:18	373:22 374:3	171:21,22	80:1,2 90:5	369:24 370:13
180:10 184:17	374:11,15,21	198:20 209:13	91:19 114:5	373:2 374:3
193:19 200:4	375:1,12,17,22	209:15 210:20	119:18 156:22	378:21 384:19
219:12 220:22	375:23,24	210:21,22	242:11 246:17	385:1,4 400:12
221:3,5 234:14	376:7,13,20	215:17 229:22	246:23 267:7	402:4 414:9,23



<b>association</b>	<b>assumed</b> 61:22	85:11,16	290:13 291:2	110:7 112:1
11:20 27:20	193:3	156:21 279:19	291:15 292:9	113:9 168:17
29:12,19 57:13	<b>assumption</b>	302:21 320:15	342:2 365:24	183:3 184:16
62:20 72:20	94:18 277:12	321:1 402:13	366:21 367:2	189:8 194:3
73:6 75:16	<b>assumptions</b>	416:1,7 417:8	368:3,21 380:5	209:15 210:16
76:6 78:12	277:14	423:15,19	382:9 427:16	210:22 270:10
80:6 91:14	<b>attach</b> 69:14	<b>available</b> 11:13	428:16,23	270:17 291:6
149:5 155:20	<b>attached</b> 205:5	14:23 56:9	430:1,10	299:3 304:24
162:20 206:15	219:7,12 220:2	63:24 64:2	<b>bachelor's</b>	333:16 416:8
212:17 223:20	252:10 433:12	71:10 103:24	383:18	418:13 420:1
226:20 227:6	435:7	113:8 115:23	<b>back</b> 10:15	426:1
227:12,13,20	<b>attaches</b> 218:23	117:21 118:2	13:22 36:22	<b>basic</b> 5:8 20:2
232:8 233:14	221:5	118:23 120:17	83:2 86:12	82:15 154:20
233:17 236:2	<b>attachment</b>	121:7 138:11	87:20 92:19	344:2 407:8,18
236:10,14	26:12	177:22 178:17	95:22 114:15	<b>basically</b> 35:6
237:12,22	<b>attempt</b> 64:11	194:19 221:20	120:15 133:5	<b>basing</b> 168:16
238:22,23	65:2 322:15	286:5 304:23	135:8 147:18	221:1
241:4,8 244:8	412:14	394:20 411:13	148:1 149:1	<b>basis</b> 22:4 39:20
244:11 251:3	<b>attempted</b>	426:14	151:14 176:9	41:13 85:6
263:7 264:12	195:10 292:13	<b>avenue</b> 3:8	180:23 181:21	114:13 135:4
264:19 265:7	<b>attention</b> 411:8	389:13	187:6,23 191:1	154:17 168:23
265:23 266:13	<b>attorney</b> 8:24	<b>avenues</b> 327:13	201:15 240:9	191:7 218:22
267:3,18	432:13,14	<b>avoided</b> 173:6	274:18 284:4	222:3 229:5,11
268:18 272:12	433:16	<b>aware</b> 34:9 45:4	300:3 316:4	230:7 231:5
272:12 274:9	<b>attorneys</b> 11:12	67:1 68:12	326:7,9 331:8	238:12 255:11
275:23 276:10	11:17 27:15,17	81:1 95:14	331:22 342:6	289:24 290:5
278:12 279:8	28:2,17 34:11	105:13 132:21	346:9 364:5,11	291:19
279:14 282:11	61:11,14 71:1	209:24 222:24	386:18 405:13	<b>Bates</b> 217:10
282:14 300:13	92:21 104:2	291:24 306:2	409:10,17	<b>Bates-number...</b>
337:13 343:14	106:16	306:14 307:20	<b>background</b>	249:14
345:17,23	<b>attract</b> 323:23	310:9,15	47:17 48:5,17	<b>bathroom</b> 35:20
346:3,7 365:7	<b>Aurora</b> 13:4,6,7	320:10 336:5	49:3 51:18	37:1,10,12
372:21 376:6,9	13:8,10,15,19	366:9 368:19	53:2 129:20	<b>Battelle</b> 281:7
382:17 390:18	<b>Austin</b> 73:10	369:21 370:2	379:5 425:16	283:10,16,17
394:14,21,22	78:23 82:23	370:11 372:23	425:24 426:4	341:14
403:20 411:15	114:22	375:9 376:17	426:12	<b>Baukholt</b> 13:1
420:19 422:13	<b>author</b> 159:24	376:18,21	<b>bad</b> 146:21	14:1
<b>assume</b> 10:7	172:13 174:21	384:6,10	282:8	<b>bear</b> 51:1
102:7,11	320:15 401:15	400:14 426:10	<b>balance</b> 146:24	<b>bearing</b> 171:1
144:15,15	<b>authored</b> 211:17	428:4,7 429:1	<b>ball</b> 247:5	304:12
202:10 212:5	<b>authoritative</b>	430:16,20	<b>barrier</b> 253:8	<b>bears</b> 249:14
249:24 377:11	20:21 21:4,9	<b>awareness</b> 417:5	259:15	<b>BEASLEY</b> 2:8
377:24 380:16	21:15	<b>B</b>	<b>base</b> 333:14	<b>beat</b> 253:10
380:22,24	<b>authority</b>	<b>baby</b> 32:13 36:8	401:16	<b>Beck</b> 394:24
381:11 382:8	225:14,22	36:15,15 42:7	<b>based</b> 42:23	395:6,8
382:12 424:8	226:3 235:16	42:12 226:2	43:11 48:4	<b>began</b> 38:7
424:15	<b>authors</b> 80:17		57:1 84:5	<b>beginning</b> 13:1

78:15,20 83:19 135:16 149:2 181:9 187:24 188:15 262:22 297:1 343:17 423:5 <b>begins</b> 71:11 75:13 124:13 135:10 148:10 148:11 204:3 226:12 235:6 252:22 281:1 341:23 400:7 <b>behalf</b> 9:2 32:17 129:18 229:24 275:6 370:5 379:13 <b>believe</b> 20:13 23:23 24:8 33:24 37:23 38:13 44:10,11 51:19 58:10 70:18,19 75:5 75:20 76:6,13 81:5,12 83:10 83:24 87:7 88:7 99:10 100:6 101:14 102:3,9 103:17 104:2,6,13 105:2 106:5 110:17 114:4 129:5,12 137:10,23 138:13 142:24 143:14,16 148:3 154:4 155:4 158:3 172:17 174:22 176:12,14 202:5 203:5,11 208:11 210:14 213:7 216:2,11 216:19 234:2 255:20 263:16 285:21 286:24 289:15 294:19	302:3 314:9 316:1 319:18 321:20 326:24 334:4 337:16 338:17 341:1,7 348:10 353:16 354:3 355:17 355:18 358:15 362:2 363:3,10 366:5,19,23 369:1 374:6,7 384:11,23 398:24 404:1 415:16 416:6 417:3,17,22 420:5 426:3,6 428:3,14 <b>believed</b> 61:24 147:1 175:7 176:23 180:15 185:3 <b>believes</b> 66:17 <b>bell</b> 162:12 <b>best</b> 38:10 65:5 281:13 295:2 360:6 432:8 <b>better</b> 145:8 161:7 191:8 198:19 331:23 <b>beyond</b> 34:16,19 99:3 213:7 221:4 231:7 241:3,3 281:11 287:18 290:17 317:11 <b>bias</b> 416:19 <b>BIDDLE</b> 3:2 <b>Bill</b> 219:9 342:7 <b>billed</b> 96:1,6 100:5 101:17 102:2 275:6,9 <b>Billing</b> 5:14,15 93:9,12 <b>binder</b> 284:16 <b>biological</b> 23:15 203:17 204:4 204:11,15	206:8,14 207:5 207:8,13,14 212:20 214:1 224:10 234:7 236:18 237:23 238:24 244:16 245:8 250:23 252:6 255:19 279:15 295:7 295:11,21 296:1 305:9 333:13 414:2,4 414:16 424:22 <b>biologically</b> 232:13,15 234:22 235:2 <b>biology</b> 130:4,4 132:12 341:20 408:16 409:4 <b>biomedical</b> 342:1 <b>biophysics</b> 341:20 <b>biostatisticians</b> 423:13 <b>BioVentures</b> 7:7 384:20 385:5 385:11,15,24 386:12 <b>bit</b> 30:19 48:20 155:5 188:13 238:17 243:4 325:20 391:4 <b>black</b> 141:23 143:8,12 <b>bodies</b> 137:17 312:21 313:5 316:22 317:12 317:18 <b>bodily</b> 135:21 136:8 137:8,13 <b>body</b> 11:19,19 16:6,12,17,22 17:16 27:11,18 28:6,14,21 29:10 30:7 31:22,24 39:2	40:22,22 41:23 42:11 43:19,20 44:20,24 56:8 57:2,11,12 62:5,10,18 63:4,6,22,24 64:2,5 66:21 67:11 80:2 107:14 112:11 113:12,16 114:6 117:3,15 117:19,24 118:4,17,23 119:18,19,23 120:24 121:18 122:19,24 123:6 138:20 140:18,20 141:3 146:7 151:9,10 167:17 227:4 228:10 233:8 236:9,15 239:18,22 241:2 242:11 245:10 247:24 248:10 254:8 254:12,23 256:7,8,15 257:23 258:1 260:18 265:12 266:24 267:16 267:16 268:12 268:24 269:19 270:11 271:11 272:2,5 274:5 274:23 283:2 300:24 314:9 314:14 316:3,6 317:5,10,11 326:17 327:2,5 328:9 329:23 329:24 335:22 344:5 346:6 370:15 378:24 389:10 395:20 411:5	<b>body's</b> 314:16 319:6 <b>bones</b> 154:8 <b>bottle</b> 429:9,17 <b>bottom</b> 146:24 202:22 322:14 354:24 <b>bought</b> 428:16 <b>boundaries</b> 130:16 133:10 247:16,19 <b>BP</b> 384:4,7 <b>Bradd</b> 13:8 <b>Bradford</b> 27:1 28:15 73:10 75:19 76:12 77:15 78:23 82:24 114:23 203:8 419:5 <b>brain</b> 314:20 <b>brand-new</b> 20:16 <b>Brands</b> 30:21 <b>breach</b> 253:7 259:14 <b>break</b> 85:23 86:2,7,16 96:8 125:16 146:16 147:11,12 148:6 201:15 204:9 224:22 240:4 280:7 283:23 285:15 293:4 331:6 362:16 363:23 364:4 369:6 <b>break-wise</b> 85:21 <b>brief</b> 50:19 86:3 206:3 285:12 426:13 <b>briefly</b> 37:17 58:11 72:4 74:24 158:13 173:19 176:15 291:23 315:16 334:23 337:10
--	--	---	--	--

338:5 371:14 373:5 387:9 390:24 391:19 391:20 398:3 418:9 <b>bring</b> 51:18 74:9 76:21 77:5 78:9 269:3 290:3 300:2 408:19 <b>bringing</b> 319:6 <b>brings</b> 26:24 34:7 54:8 <b>broad</b> 2:4 36:1 52:9,15 56:4 120:21 129:24 226:23 296:4 310:22 <b>broader</b> 104:1 <b>bronchial</b> 321:9 <b>brought</b> 112:18 <b>browed</b> 271:18 <b>brush</b> 340:5 <b>brushed</b> 316:12 320:10 330:9 <b>bulleted</b> 68:22 <b>burden</b> 227:14 <b>buried</b> 394:1 <b>buying</b> 429:5	<b>California</b> 2:21 <b>call</b> 317:21 421:3 <b>called</b> 80:15 81:22 82:14 388:13 419:5 <b>calling</b> 181:3 <b>Campus</b> 3:3 <b>Canada</b> 6:10 7:2 104:24 105:9 105:10,16,21 106:2 201:17 201:24 202:9 202:17,18 204:15,21,24 206:7 207:15 208:2 346:9,20 347:3,15 348:1 348:13,23 349:3 <b>cancer</b> 6:8 9:5 11:16,22 27:21 29:14,20 30:13 42:22 45:9 57:14 62:22 65:21 66:24 68:9 88:1 91:3 91:14 130:4 141:21 149:6 153:18 197:6 197:17 198:5,8 198:10 199:7 199:12 200:8 207:2 212:19 218:15 222:21 226:16 227:22 228:1 233:15 236:11 242:14 244:9 245:4,13 246:19 247:1 248:24 252:24 257:3 264:21 265:24 268:19 275:24 293:21 306:19,24 307:11 308:6 308:16 310:14	330:13,18 331:15 333:10 334:18 335:1 335:11,22 336:21 337:7 337:14 343:15 345:17 355:16 355:20,24 356:5 365:8 369:14,24 370:7,13,16 372:21 373:2,8 373:17,18,23 374:4,10 375:1 375:9,12,18 376:8,10 378:1 378:15,21,24 379:2 381:3,17 382:18 390:18 397:22 398:5,8 403:21,24 411:16 426:9 430:18 <b>cancers</b> 228:13 326:20 336:6 356:5 <b>capital</b> 321:15 321:16 <b>captions</b> 12:21 <b>carbon</b> 141:23 143:8,12 158:21 159:4 159:12 182:16 183:5 189:21 <b>carcinogen</b> 355:12,14,15 356:3 366:10 <b>carcinogenesis</b> 7:9 218:13 226:13 231:1 232:10 336:12 338:4 398:18 <b>carcinogenic</b> 305:24 306:10 307:7,16 309:19 310:6 324:15 366:8	<b>carcinogenicity</b> 210:21 227:19 330:21 338:9 339:4 403:23 <b>carcinogens</b> 355:6 356:22 <b>carcinomatous</b> 163:12 <b>Care</b> 3:15 <b>career</b> 33:13 <b>carefully</b> 433:4 <b>carry</b> 430:17 <b>Casarett</b> 20:19 20:24 21:10 22:1,16 25:11 25:14 26:20 45:24 408:9 409:16 410:7 <b>cascade</b> 207:1 317:21,21 318:22 319:8 324:24 325:12 325:18,19 330:20 <b>cascades</b> 319:14 <b>case</b> 15:1,19,24 16:16 26:23 30:15 32:11 42:21 53:22 57:10 61:23 96:19 118:1 119:6 130:17 133:9 139:5 145:5 165:18 178:6,11,15 212:11 229:19 230:15 263:21 265:10 266:10 268:16 285:1 289:19 324:19 340:8 343:5 355:5 370:5 377:3,7 382:3 <b>case-control</b> 294:11 417:15 418:3,7,14 <b>cases</b> 1:8 13:15	13:23 158:20 <b>cast</b> 194:22 <b>causal</b> 11:20 27:2,19 29:12 29:18 57:13 62:20 76:5 78:12,21 82:14 84:4,12 91:13 119:12 122:4 155:20 212:17 226:21 232:8 233:14,17 236:2,10 237:12,22 238:22,23 241:4,8 244:11 246:24 264:19 265:1,7,14,23 266:13 267:3 267:17 268:17 275:22 300:13 300:23 301:1 337:13 343:14 345:17,23 346:2,7 365:6 372:20 376:6,9 381:15 382:16 390:18 394:14 394:21,22 403:20 <b>causality</b> 228:19 230:22 231:20 240:19 279:20 <b>causally</b> 30:12 66:23 242:13 <b>causation</b> 72:20 75:16 79:13 80:6 155:6,7 155:10,15,21 237:7 239:13 246:12,17 299:6 379:16 379:17 393:13 <b>causative</b> 73:7 218:15 222:21 <b>cause</b> 74:10 75:23 79:1
<hr/> <b>C</b> <hr/> <b>C</b> 2:1,19 3:1 6:18 284:12,15 284:20,24 285:19 286:2,4 286:19,22 287:11 288:3 289:13 366:13 367:5,15,18 373:20 <b>C-U-B-A-N-S-...</b> 97:14 <b>C.F.R</b> 5:10 50:4 <b>calculating</b> 411:4 <b>calculation</b> 122:14				

91:5 92:7	84:20 128:8	17:18,24 18:3	85:3 105:11	258:23 271:5
112:15 120:11	133:3,15 136:5	323:15 409:13	118:1 135:4	285:9 346:1,11
163:12 207:2	138:7 139:3	409:15	137:10 144:5	359:19 387:1,6
220:14 221:10	157:11 163:3	<b>Charles</b> 2:5 9:1	145:4 150:19	389:22 390:9
241:16 299:21	204:20 209:24	<b>chart</b> 98:21	158:10 162:8	390:21 391:8
300:1 311:4	225:6 229:8	285:18 368:19	183:17,23	392:8 395:2
312:22 313:6	230:21 231:18	379:20 400:8	184:2 188:5,21	405:1
325:10 333:9	258:22 302:9	<b>charts</b> 367:19	189:13,15,15	<b>cites</b> 22:4 85:3
373:7,22	312:20 313:4	368:16	190:17 191:2	176:8,11
375:18 378:1	313:16 316:20	<b>check</b> 71:13	192:10,14,20	180:11 189:2
378:15 406:2	317:18 325:10	83:20 85:19	196:9 200:20	390:20,22
407:7,14	355:23 374:2	273:22 274:1	200:24,24	391:6,14 392:7
<b>caused</b> 106:6	379:11 387:5	302:8 353:23	206:4 208:9,11	392:9,13
162:11 305:19	396:10 407:17	428:18	208:12 215:19	<b>citing</b> 84:8
356:4 374:24	411:12,17	<b>checking</b> 98:5	220:22 234:20	151:16 153:21
375:1	413:18 414:22	<b>chemical</b> 18:19	237:10 240:2	200:14 235:5,7
<b>causes</b> 227:21	415:22	19:18 23:14	251:18,24	239:19 263:24
304:7 307:8	<b>CERTIFICA...</b>	92:4 139:16	252:9 253:19	281:7 302:24
309:20 310:8	4:9 432:1	164:20 165:2	255:9,12,20	354:8
310:10 356:5	<b>Certified</b> 1:18	210:11 312:5	256:12,14	<b>citizen</b> 16:19
369:13 370:6	1:20 432:2,3	318:10 323:22	258:21 277:9	52:6 53:20
<b>causing</b> 206:10	432:19,20	<b>chemicals</b> 7:5	286:11 290:15	<b>claim</b> 189:1
406:1 407:6	<b>certify</b> 432:3,6	19:8 130:7	291:12,22	390:21 391:11
<b>cavity</b> 165:4	432:10,12	338:18 351:15	302:5 327:11	391:12 392:7
168:9 228:6,9	435:4	353:5 354:20	350:18 352:4	<b>claims</b> 279:19
229:1 281:10	<b>cervical</b> 162:18	<b>chemistry</b> 130:4	354:13,13	<b>clarified</b> 181:4
326:16	253:8 259:15	<b>child</b> 36:12	357:21 358:11	<b>clarify</b> 31:13
<b>cell</b> 405:18	<b>cervix</b> 161:4	428:17	358:14,17,20	55:20 134:17
408:1	163:13 281:10	<b>choice</b> 428:22	392:17 395:8	184:23
<b>cells</b> 306:4 314:1	<b>challenge</b> 95:2,4	<b>chose</b> 103:22	412:2 415:20	<b>clarity</b> 100:17
314:6 316:21	95:18 96:15	<b>chronic</b> 400:12	<b>cited</b> 70:19 71:5	114:5
323:24 330:4	99:24 102:2	402:3	78:4 105:16	<b>class</b> 417:6
344:4 404:5,8	155:13	<b>cigarette</b> 227:24	137:6 141:24	<b>classically</b> 24:8
<b>center</b> 319:6	<b>chance</b> 158:11	<b>ciliary</b> 253:10	144:21 145:15	24:22
<b>central</b> 313:10	173:10 176:18	<b>circumstances</b>	146:4 154:12	<b>classification</b>
313:19 314:4	177:3,12,12	298:11 299:19	168:2,22	7:4 351:14
321:16	178:2 179:10	312:20 351:19	177:18 184:21	353:4 354:2,20
<b>certain</b> 164:21	183:1,4 200:2	418:5 420:6	187:21 188:6,8	<b>classified</b> 355:13
272:3 305:20	277:23 304:14	<b>citation</b> 142:24	188:10,16,17	355:22 366:10
<b>certainly</b> 22:3	419:15	235:16 352:12	189:1,2 190:20	375:9
24:14 25:5	<b>change</b> 246:4	352:13 359:7	190:22 191:9	<b>classifying</b>
40:6 41:10,22	266:24 434:2	<b>citations</b> 168:15	205:10,24	218:14 222:20
42:9,10 44:7	<b>changed</b> 245:15	182:1 200:15	212:2,4 219:18	<b>clear</b> 9:23,24
48:3 63:21	<b>changes</b> 163:12	255:1	230:6 236:22	10:4,7 23:1
64:11 65:2,12	433:11 435:6	<b>cite</b> 20:13 22:1	237:21 251:8	47:2 111:12
69:15 72:24	<b>changing</b> 272:6	28:10 32:2	253:17 254:15	132:9 138:3,24
78:16 81:17	<b>chapter</b> 5:6	72:20 73:4	255:7 256:23	140:5 167:9

171:20 195:2	<b>come</b> 42:21 44:2	219:13 221:3,6	<b>complications</b>	123:2 131:14
208:15 247:2	83:2 89:13	221:15 222:5	148:14	172:24 218:20
252:5 269:15	92:19 95:22	342:22	<b>component</b>	218:23 238:11
290:10 338:24	104:19 122:14	<b>communicatio...</b>	357:9 358:6	238:12 256:17
360:9 363:14	130:5 196:3	264:5 294:5	413:4,15,24	272:4 277:14
385:23 397:8	262:2 267:20	<b>communiqué</b>	<b>components</b>	367:12 389:12
420:17 422:11	323:6,7 336:17	219:22 220:19	255:4 313:12	402:10 405:5
<b>clearance</b>	364:5 420:7	<b>companies</b> 7:7	356:17 381:4	<b>conclusive</b>
152:17	<b>comes</b> 70:3 75:6	53:19,19,24	382:14	228:18 235:24
<b>cleared</b> 325:2	131:18 298:14	54:14,20 55:7	<b>composition</b>	236:2 257:15
<b>clearer</b> 132:8	301:23 304:23	385:12,15,20	310:19 311:18	<b>condemned</b> 84:5
<b>clearly</b> 91:11	427:7	386:13	312:15 321:8	<b>conditions</b>
268:21 324:7	<b>comfortable</b>	<b>company</b> 34:13	<b>compound</b>	158:21 162:18
339:11 400:9	130:14 133:8	34:23 35:8	355:8 405:24	313:4
402:1	133:12 194:4	48:6,23 49:1	407:6 408:13	<b>conduct</b> 38:7
<b>cleavage</b> 371:19	296:13 339:9	52:3 53:4,15	409:1	39:15 44:15
371:22,23	402:18	54:8,10 66:7	<b>compounds</b> 19:2	58:19
372:1	<b>comfortably</b>	95:9 98:21	<b>comprehensive</b>	<b>conducted</b> 38:21
<b>clerical</b> 100:8,24	296:14	99:2 342:2	64:11	113:7 148:12
<b>Cleveland</b> 3:9	<b>coming</b> 37:17	384:14	<b>computer</b> 124:4	148:21 149:9
<b>clip</b> 284:16	201:12,13	<b>comparable</b>	<b>concentration</b>	287:24
<b>close</b> 89:14	256:20 422:1	289:21 290:4	355:2	<b>confidence</b>
146:15 162:20	<b>comma</b> 359:6	<b>compare</b> 60:7	<b>concept</b> 128:15	296:20 420:21
280:6 281:9	<b>commencement</b>	144:24 315:3,4	421:3	422:16
359:6	432:4	<b>compared</b>	<b>Concepts</b> 82:15	<b>confidential</b>
<b>closed</b> 69:1	<b>commencing</b>	286:10 327:14	<b>concern</b> 149:5	54:23
142:18 218:8,9	1:17	329:23 342:13	<b>concerned</b>	<b>confidentiality</b>
369:15	<b>comment</b> 84:20	<b>comparing</b>	425:17	55:3,11
<b>clue</b> 423:17	100:13 229:22	98:20	<b>conclude</b> 39:22	<b>confirm</b> 182:11
<b>Code</b> 50:14,17	262:23 329:10	<b>compelling</b>	114:11 163:10	411:11 415:20
50:20	329:11 331:1	218:6 221:22	418:14 420:18	<b>confirmed</b>
<b>Coherence</b>	419:16 423:4	<b>competently</b>	420:22 422:12	190:14
207:16	<b>comments</b> 49:20	122:16	422:17	<b>conflict</b> 229:24
<b>cohort</b> 411:20	166:1 272:21	<b>competing</b>	<b>concluded</b> 142:8	420:23 422:18
412:1,5,9,10	322:5	120:19 121:8	187:5 194:8	<b>conflicts</b> 230:14
418:3	<b>Commerce</b> 2:9	121:11	282:10	<b>confound</b>
<b>colleague</b> 99:13	<b>commission</b>	<b>complete</b> 11:7	<b>concludes</b> 73:18	154:24 156:2,4
<b>colleagues</b> 99:5	432:22 435:17	63:20 70:8	431:15	<b>confounded</b>
<b>collect</b> 287:11	<b>Committee</b> 2:6	79:11 116:17	<b>conclusion</b> 40:3	152:16,22
<b>collection</b>	2:11,17	137:22 191:19	40:16,21 41:16	153:5 154:18
270:18	<b>common</b> 38:17	299:13	41:20 172:22	157:3,7
<b>column</b> 161:9	39:18 125:6	<b>complex</b> 316:13	189:6,8 227:21	<b>confounding</b>
164:23 223:19	126:2	323:22 330:3	237:12 257:14	153:1,12,13,17
<b>Combine</b> 218:8	<b>commonly</b>	<b>complexities</b>	267:21 290:1	153:24 154:7
328:3	20:24 21:7,15	320:12	418:6,11 419:5	154:21 155:5,8
<b>combined</b>	<b>communication</b>	<b>complicated</b>	432:11	156:11,14,19
424:23	168:8 218:20	327:19	<b>conclusions</b> 43:5	257:4



<b>confronted</b> 317:5	55:17 248:11	247:12,23	351:5	367:17 372:8
<b>confused</b> 95:20	<b>consistency</b> 203:16 227:6	250:9,15	<b>copy</b> 18:5 50:13	383:4,8 418:10
246:9	227:12 417:21	256:22 257:10	71:1 81:10	423:20 425:24
<b>conjunction</b> 136:18	417:23	261:6,7 262:16	96:10 105:3	435:5
<b>connection</b> 29:5	<b>consistent</b> 182:20 242:5	265:20 272:22	106:15,17	<b>corrections</b> 433:4,7 435:6
150:22 167:24	263:19 264:9	273:1 274:20	162:2 197:24	<b>correctly</b> 18:21
225:14 251:4	410:7 417:15	275:3,16	273:16 293:17	18:22 22:13,14
349:19 385:23	<b>consistently</b> 381:13	283:11 298:10	340:21 408:21	76:1 88:5,7
<b>conscious</b> 428:15	<b>constituent</b> 14:19	298:23 299:2	415:7	102:7,11
<b>consecutively</b> 217:12	<b>consulting</b> 384:2	300:1,11,15,24	<b>corn</b> 428:4	107:18 114:3
<b>consequences</b> 22:11 46:3,12	<b>consumer</b> 263:7	318:22 325:13	<b>cornstarch</b> 428:8,12,23	135:24 136:2
<b>Consequently</b> 173:4	264:13 272:13	338:12 399:7,8	<b>corporate</b> 18:8	148:16,17
<b>consider</b> 16:1	274:9 276:11	399:13 401:8	419:24	149:12 152:20
20:19 21:3,23	281:21 287:18	401:18 405:11	<b>correct</b> 11:1	152:21 173:7,9
56:17 59:7	<b>consumers</b> 16:19 52:6	<b>continue</b> 39:14	15:7 20:14	206:19 218:16
72:22 103:9	53:20	124:20 136:2,4	26:21,22 29:23	218:18 231:9
129:17 145:14	<b>contact</b> 33:2	152:13 392:9	44:16 45:2,12	243:17 253:12
205:20 240:16	45:1 52:22	429:12	45:13 48:19	253:14 263:9
240:19 241:11	<b>contacted</b> 32:16	<b>continues</b> 124:22 161:17	58:20 71:12	263:15 276:15
244:3 246:12	32:19 39:24	181:9 279:21	73:21 76:22	321:18 322:11
254:1 345:19	<b>contain</b> 374:14	324:24	79:11 83:9	<b>correlative</b> 73:6
431:4	377:16 381:12	<b>contractibility</b> 171:11	87:8 102:14	<b>correspondence</b> 281:17 283:6
<b>consideration</b> 160:6	<b>contained</b> 382:10	<b>contractility</b> 170:22 171:15	104:17 108:3	304:12 328:14
<b>considerations</b> 84:11	<b>contains</b> 365:10	171:24	108:16 109:11	<b>cosmetic</b> 30:21
<b>considered</b> 5:17	377:13 380:7	<b>contribute</b> 305:24 306:9	109:15 110:16	31:5 51:1
15:4 63:4	<b>content</b> 216:16	307:7,16	114:24 115:6	149:4 225:15
102:21 103:5	365:23 367:1	309:18 310:6	115:16 116:15	225:21 250:24
104:21 115:5	<b>contents</b> 201:2	337:5	116:16 117:6	252:7 255:20
158:7 164:9	<b>context</b> 51:10,12	<b>controversy</b> 384:7	135:2 162:13	257:16 291:2
166:7 167:24	79:7 82:21	<b>conveniently</b> 158:4	172:17 174:8	<b>coughing</b> 323:3
170:24 174:24	113:17 115:9	<b>conversation</b> 220:23	177:22 181:2	<b>counsel</b> 2:6,11
191:13,15,21	123:5 127:10	<b>conversations</b> 61:9	181:20 183:16	2:16,22 3:5,10
192:12 193:10	135:16 136:11	<b>converse</b> 295:23	183:17,19	3:15 8:12 12:1
196:4 199:17	137:8 144:9	298:8	186:24 187:21	93:18 351:6
204:14 254:13	145:21 156:3	<b>Cook</b> 285:9,19	187:22 188:16	432:13,14
256:8 257:24	156:15 157:10	285:24 286:5	202:20 204:17	<b>Counselor</b> 399:24
345:4 349:2,4	157:13 177:2	286:10 287:13	207:5 215:6	<b>count</b> 411:10
371:13 386:24	227:4 230:5,20	287:19	216:19 225:7	<b>couple</b> 93:5
<b>considering</b>	234:8 237:8,15	<b>copies</b> 340:17	248:2 253:19	228:21 394:23
	245:9,10 247:9		267:10,22	405:4 423:21
			270:21 275:13	<b>course</b> 21:19
			282:21 284:13	47:2 81:14
			285:17 288:21	203:8 284:24
			332:2,15	288:14 289:9
			345:20 347:12	

318:9 346:11 428:17 <b>court</b> 1:1,18 8:14 357:14 432:3,20 433:20 <b>courtroom</b> 70:9 336:18 <b>cover</b> 20:8 82:8 318:7 327:22 352:24 353:3 363:9 <b>covers</b> 21:10 138:18 <b>Covestro</b> 13:5 14:16 <b>Cramer</b> 176:12 <b>creation</b> 367:15 <b>criteria</b> 27:5,21 28:4,20 29:24 72:6 73:2,3,9 73:11 78:11 79:5,6,9,12,23 79:24 82:14 84:11 113:18 115:8,10 203:7 203:23 211:12 212:20 227:1,2 227:14,16 233:12 236:16 236:17 237:5,5 243:5 300:3,8 333:14 419:6 <b>critical</b> 185:16 185:18 187:10 303:20 <b>criticism</b> 60:21 347:14 <b>criticisms</b> 348:14 350:3 <b>criticize</b> 303:19 <b>criticizing</b> 186:23 <b>CRR</b> 432:18 <b>crude</b> 289:19 <b>cry</b> 75:16 80:6 <b>CTEH</b> 5:14,15	34:5 37:21 38:11 63:11 93:9,12 95:1,6 95:15,23 96:13 97:9 99:22 101:4,16,24 102:12 289:10 312:3 383:21 383:24 384:11 384:19 385:1 385:13,18,24 419:21,24 <b>CTEH's</b> 384:7 <b>CTFA</b> 261:23 263:2 272:18 273:2,5 282:22 283:13 <b>CTFA's</b> 281:13 <b>Cubanski</b> 97:12 287:1 <b>cuff</b> 324:8 339:10 344:9 <b>culminating</b> 285:11 <b>cup</b> 126:11,24 <b>curiosity</b> 41:4,7 428:17 <b>Curriculum</b> 5:9 26:9 <b>cursor</b> 11:6 38:24 39:4,5 169:5 177:24 292:20 <b>cut</b> 79:20 130:12 <b>cutoff</b> 355:6 356:22 359:20 359:21 <b>cutting</b> 375:23 <b>CV</b> 26:15 <b>cytokines</b> 314:1 330:4 <b>cytotoxic</b> 340:10 342:11,16 343:4,8 344:3 345:20 <b>cytotoxicity</b> 339:5,14 344:9	346:5 <hr/> <b>D</b> <b>D</b> 405:17 <b>D.C</b> 3:14 <b>daily</b> 427:17 <b>Dana</b> 97:11,23 287:1 <b>dash</b> 135:22 <b>data</b> 54:15 55:5 64:16 131:12 145:3 146:8 170:3 177:4 181:9 188:24 189:18 200:5 200:13 208:8 214:2 229:13 231:7,15 233:1 235:21,23 236:1,9 238:11 248:20 255:8 256:5,15,16 268:3 269:7,8 269:18 270:18 270:19 272:19 274:20 277:12 277:13,16,17 277:21 278:3 279:17 283:8 286:5,9 287:12 288:2 296:6,10 298:12,15,23 299:2 300:19 300:19 301:7 301:12,16 302:21 342:12 360:4 362:9 373:3 382:13 390:20 391:5 392:6,13 394:22 413:23 423:6 <b>databases</b> 66:3 <b>dataset</b> 248:20 <b>datasets</b> 254:18 259:3 <b>date</b> 1:17 8:6	220:2 225:4 262:24 432:8 433:9 435:12 <b>dated</b> 82:24 282:1,7 432:23 <b>Daubert</b> 95:2,3 95:18 96:14 99:23 102:1 155:12,13 <b>David</b> 3:21 8:4 <b>day</b> 20:17 96:7 198:18 224:11 428:1,3 435:16 <b>days</b> 433:16 <b>deal</b> 387:23 <b>dealing</b> 30:21 64:14 98:12 159:4,5 191:24 406:12 <b>Dear</b> 342:7 <b>DEBBIE</b> 3:18 <b>decide</b> 106:6 298:16 301:8 <b>deciding</b> 42:6 <b>deciphered</b> 276:14 <b>decision</b> 124:6 287:5,9 428:11 428:15 <b>decision-maki...</b> 84:8 <b>decisions</b> 421:2 422:6,21 <b>dedicated</b> 411:5 <b>deduce</b> 94:15 <b>deemed</b> 433:19 <b>deep</b> 161:2,16 <b>deeply</b> 162:19 <b>defend</b> 61:12 <b>Defendants</b> 2:22 3:5 <b>defense</b> 61:14 104:3 137:15 140:19,22 141:3 314:8,11 314:15,16,24 315:4,8,9,19	315:20 317:3 322:21 323:12 329:22 330:1 332:1,5,7 <b>defer</b> 134:4,5,22 <b>define</b> 311:13 324:7 339:11 344:8 359:23 402:18 <b>defined</b> 57:22 <b>defining</b> 150:13 <b>definitely</b> 138:20 300:7 413:24 <b>definition</b> 23:22 57:24 58:1 151:23 154:21 156:3,5,10 249:23 250:1 324:10 350:13 352:1,9 353:14 353:17 354:8,9 356:13 357:2 357:16,23 359:1,4,12 360:14 403:3,4 404:3 <b>definitions</b> 364:20,24 371:12 <b>degree</b> 97:21 <b>degreed</b> 97:17 <b>degrees</b> 314:11 <b>demonstrate</b> 263:6 264:12 272:11 278:11 278:16,17 279:7 282:14 400:10 402:1 <b>demonstrated</b> 279:20 281:8 <b>demonstrates</b> 274:8 276:4,10 <b>Department</b> 225:5 <b>depend</b> 24:19 56:10,13 58:12
--	---	---	--	---

59:10 157:9	189:22 197:5	84:13 88:9	169:10,12	161:23 168:7
214:12,19	201:16 217:14	106:14,19	335:11 336:20	226:10,12
297:19 298:10	218:10 224:17	127:13 129:15	337:6 403:24	230:24
299:24 318:10	249:10 261:12	131:10 133:1	<b>developments</b>	<b>direct-to-cons...</b>
324:17,19	273:11 276:18	137:12,20	178:13	54:4
343:9 388:8	280:2 284:19	169:4 176:19	<b>develops</b> 335:22	<b>directed</b> 146:2
389:7 395:14	293:6 313:20	178:3 200:3	<b>diameter</b> 126:13	170:22 171:14
398:5,11 399:6	320:16 322:15	207:20 211:7	<b>diapering</b> 428:1	171:23
403:13 407:12	328:4 340:14	211:10 216:3	428:2	<b>directly</b> 47:20
<b>depending</b> 25:3	347:24 351:12	245:9 261:1	<b>difference</b>	49:7 53:18
156:20 288:6	362:12 364:15	290:17 292:4	271:19 292:3	77:11 78:3
311:4 317:16	372:3 386:11	298:1 337:18	417:2 420:18	397:4 410:3
318:10 397:2	391:4 398:16	338:17 342:12	422:13	<b>director</b> 219:8
<b>depends</b> 24:7,19	400:13 402:4	347:19 354:23	<b>differences</b> 59:1	<b>dis-</b> 79:5
51:24 52:10	408:10 415:8	368:10,13	<b>different</b> 75:8	<b>disagree</b> 22:22
92:12 117:23	419:10 431:16	374:16 376:23	75:13 76:3	22:24 23:9,19
224:10 296:5	431:20 432:11	380:21	80:4 92:16	51:13 84:14
298:11 299:8	433:3,13,17,18	<b>detailed</b> 306:17	94:6 121:14,15	168:18,24
299:11 311:22	<b>depositions</b>	314:23 315:7	122:7,17 125:9	180:2 229:8,11
312:18,18,19	104:7 105:3	315:17 316:12	126:15 127:23	234:6 272:24
313:1 342:19	202:10,14	334:20 335:2	127:23 128:21	273:22 274:12
390:5 395:24	<b>deps@golkow...</b>	393:5 394:2	130:2,5 137:24	274:14 275:1
<b>depiction</b>	1:24	<b>details</b> 273:6	149:20 153:23	275:11,14
406:23	<b>depth</b> 58:11	<b>detections</b>	156:20 165:14	276:19 277:1
<b>deponent</b> 4:11	128:24 177:4	289:20 368:6	176:8 185:23	278:7 360:12
8:11 435:1	205:19 291:16	<b>determination</b>	209:13,20	360:23 407:22
<b>deposed</b> 9:19	304:15 319:17	76:5 78:12	214:17 246:8	421:7 422:23
<b>deposing</b> 433:15	337:15,21	122:4 263:5,18	253:20 288:6	423:10 426:19
<b>deposit</b> 310:19	387:7	279:6	288:12 290:11	427:3,11,12,21
311:18 312:15	<b>describe</b> 142:6	<b>determinations</b>	290:19 302:11	431:12
312:21 313:5	157:14 295:2	238:21 272:20	313:12 314:1	<b>disappeared</b>
321:8	295:19 328:22	<b>determine</b> 11:19	314:10,10,11	416:14
<b>deposited</b> 165:3	418:16	29:17 30:9	314:15,18,23	<b>discovered</b>
165:13 182:17	<b>described</b> 23:22	43:10 55:15	325:20 330:4	40:11
183:6	27:14 163:14	79:1 214:21	331:18 387:15	<b>discuss</b> 21:21
<b>deposition</b> 1:14	200:2 240:20	255:11 349:20	397:1 406:22	27:23 30:1
5:1 6:1 7:1 8:8	268:8	403:17	<b>difficult</b> 253:5	72:2,4 88:7,8
9:6 12:3 17:17	<b>describing</b>	<b>determined</b>	259:13	88:23 89:20
20:1 26:8 34:1	414:12	103:7,15 356:4	<b>ding</b> 201:11	116:4 117:12
34:2 50:3	<b>DESCRIPTI...</b>	<b>determines</b>	<b>dioxide</b> 141:23	125:10 126:5
72:10 82:1	5:3	271:17	143:9,12	129:14 132:2
93:8,11 102:19	<b>descriptive</b>	<b>determining</b>	<b>diploma</b> 262:17	133:16,17
104:14 107:3	408:11,23	55:24	<b>Diplomate</b> 1:19	151:12 153:10
141:8 157:19	<b>design</b> 367:15	<b>developed</b>	262:10,15	153:22 169:4
159:18 164:11	<b>despite</b> 377:23	300:16 334:11	432:2,19	173:19 178:22
166:14 170:12	<b>destroy</b> 322:16	<b>development</b>	<b>direct</b> 148:7	179:16 191:8
172:7 174:15	<b>detail</b> 22:21	9:5 163:4,9	158:15,16	211:7 297:13

319:1 327:7	152:11 165:16	<b>distracted</b> 124:5	<b>document</b> 1:7	285:18,23,24
330:5 338:5	179:14 195:20	<b>DISTRICT</b> 1:1	12:8 50:7,9,12	286:6,11,13,17
347:18,19	230:16 235:10	1:1	50:13,23 72:8	287:17 288:20
348:22 350:7	242:16 243:19	<b>dive</b> 38:24 39:4	82:18 102:24	290:10 292:8
354:22 365:22	243:23 252:20	39:5	103:1 143:15	293:3,13
368:9,12	255:2 274:18	<b>diverse</b> 327:18	144:8 146:6	344:17 347:9
371:24 383:2	274:22 294:7	<b>doctor</b> 10:21	162:4 164:4	347:18 366:12
389:17 403:12	308:4 311:10	11:11 14:15	180:17 187:15	366:14,18,24
411:21 418:9	319:14 322:22	19:11 21:18	198:12 204:21	400:20
426:3	325:24 326:2	27:24 35:18	204:24 208:19	<b>doing</b> 39:17 40:6
<b>discussed</b> 24:9	327:15 330:7	38:21 47:24	217:9,13,19	43:4 46:10
32:7 37:20	338:17 342:21	49:23 50:12	221:10,16	85:20 119:23
104:23 105:1	342:23 371:10	59:5 67:19	228:22 230:4	122:13 124:8
106:13,19	388:9 389:13	68:19 77:14	230:19 231:10	156:21 193:15
111:24 113:12	<b>discussion</b> 85:8	86:15 88:12	233:24 234:4	198:19 221:17
114:21 118:20	115:18 127:6	94:21 103:2	257:11 273:5	222:6 231:11
139:12,15	127:17 128:12	112:5 120:3	276:6 277:16	236:21 242:10
148:6 152:24	145:21 158:18	121:6 127:15	277:21 280:22	295:16,17
153:11 169:3	161:8 175:5,15	137:7 141:13	285:3 286:23	296:8 318:15
176:13 178:8	180:5,10,10	147:21 150:3	287:12 288:7	338:20 342:14
203:9 207:20	181:8 186:15	156:12 170:18	293:10 328:1	350:24 409:21
210:8 219:3,5	188:2 202:9	175:2 180:6	341:18 344:10	410:16 430:21
233:3 234:9	204:8 214:7	184:22 196:16	344:16 347:22	433:8
240:22 252:3	252:22 257:7	198:4 201:23	349:20 350:18	<b>dominant</b> 171:2
265:21 272:1	285:12 339:14	205:6 208:24	350:22 352:21	<b>dose</b> 17:13 24:11
290:2 304:7	343:18 371:18	209:12 213:13	353:1,7,11,14	24:12,23,24
319:5 326:9	379:18 393:5	218:17 221:9	353:21 354:1	92:15 305:20
329:21 332:22	394:3 402:10	229:18 234:18	354:10 356:12	312:19 313:2
336:11 337:15	412:13,19	236:3 239:2	359:11 360:13	317:17,23
338:23 339:3	415:14 426:13	240:12 245:14	360:20 362:3	318:3 325:10
346:5,10	427:13	257:21 263:10	362:23 364:6	343:24 387:17
355:17 365:2	<b>discussions</b>	268:7 277:19	386:5 400:19	411:22 412:5
366:2 371:14	61:10 405:5	284:7 289:1	401:15,18	412:15 413:4
371:15 372:9	<b>Disease</b> 72:19	302:17 306:21	402:9 404:3	413:15,24
374:10 387:2	<b>diseased</b> 252:14	307:12 308:10	423:6	414:2,5,10
391:4 392:22	253:4 260:5	318:22 330:15	<b>documented</b>	<b>dose-response</b>
395:15 398:3	<b>diseases</b> 148:14	331:10 333:7	96:2 206:12	413:1,12 414:6
405:15 412:9	164:21	351:21 353:6	<b>documents</b>	414:8 415:4
<b>discusses</b> 65:4	<b>dismiss</b> 223:22	353:12 357:4	50:21 68:6	416:3,8
142:5 143:18	<b>disprove</b> 79:13	357:14 360:13	69:1,5,21	<b>dose-responsive</b>
224:8 256:24	118:16	361:20 364:14	70:11,12 93:16	414:13,17
257:4 291:13	<b>disregarded</b>	369:4 370:1	103:24 145:2,5	<b>dots</b> 172:15
336:9	163:24	373:8,23 382:3	151:8 188:23	<b>double</b> 172:15
<b>discussing</b> 16:3	<b>distinction</b>	386:21 398:21	188:24 208:7	<b>double-check</b>
46:7 59:1 60:4	245:22 246:6	402:6 403:12	216:9,10,12,24	76:23
89:19 118:3	<b>distinctly</b>	404:6 405:12	217:6 235:19	<b>double-checki...</b>
130:15 149:18	305:11	407:3 417:7	238:9 285:8,11	98:5 398:23

<b>doubt</b> 227:20	322:24 384:11	321:19 325:19	414:3,3,4	<b>employ</b> 48:7
<b>Doull</b> 20:20	<b>drafting</b> 96:19	326:9,11 330:9	<b>efforts</b> 421:2	59:7 145:20
<b>Doull's</b> 20:24	<b>drew</b> 185:6	344:7,17 366:2	422:6,20,20	<b>employed</b> 203:7
21:10 22:1	<b>drill</b> 290:24	367:16 371:10	<b>Egli</b> 5:19 157:20	<b>employee</b> 96:8
<b>downward</b>	<b>DRINKER</b> 3:2	383:23 389:8	158:6,6,19	432:13,14
135:20 136:8	<b>Drive</b> 3:3	391:4 393:13	160:1,13 182:5	<b>employs</b> 46:22
136:10 137:8	<b>DRONETT</b> 3:18	405:16 408:10	182:8,13,15,21	47:1,11,20
137:13	<b>Drs</b> 183:21	<b>early</b> 383:10	183:2,10,16,21	<b>encompassed</b>
<b>Dr</b> 8:21 9:22	285:19,24	<b>easier</b> 220:6	183:21 184:5,9	387:19
26:24 33:18,20	286:10 303:7	<b>easily</b> 192:5	187:24 188:15	<b>encompasses</b>
97:23 99:1,8	366:23	<b>EASTERN</b> 1:1	189:20	130:1
99:14,18,21	<b>Drug</b> 225:3,6,11	<b>ecosystem</b> 23:16	<b>eight</b> 136:15	<b>encountered</b>
101:3,19	225:13 226:3	<b>edition</b> 5:13	<b>eighth</b> 20:13	388:10
107:12 108:2,4	<b>due</b> 152:18	20:12,13,15	<b>Eighty-Eight</b>	<b>endeavors</b> 81:16
108:12,22	171:1	22:18 23:2,4,8	13:3	<b>ended</b> 228:15
109:4,12,14	<b>duly</b> 8:18 432:4	25:14 81:23	<b>either</b> 17:13	421:16 429:8
110:2,3 124:14	<b>duration</b> 403:11	82:3	32:20 79:5,10	<b>endometrial</b>
135:11,17	412:22 413:3,7	<b>educated</b> 144:17	79:12 104:14	228:9 326:15
136:16 142:5	413:8,12,15,23	<b>education</b> 21:2	107:14 163:13	<b>endpoint</b> 40:7
158:6 183:21	414:23 416:4,8	48:5,16 129:19	169:8,9 190:15	<b>ends</b> 325:17
185:16,19,20	<b>dust</b> 322:15	138:14 270:17	202:14 208:8	421:5,17
186:5,14,18,23	<b>dusted</b> 199:13	292:18,21	<b>election</b> 427:15	<b>engineering</b>
187:11,14	<b>dysfunction</b>	<b>educational</b>	<b>element</b> 298:15	122:7,13
223:23 254:20	152:17	81:16	<b>elevated</b> 395:4	<b>engineers</b>
259:9 261:10	<hr/>	<b>effect</b> 25:2 74:10	395:11	122:13
261:15,16	<b>E</b>	75:24 79:1	<b>elicit</b> 228:10	<b>enter</b> 213:21
285:9,9 287:13	<b>E</b> 1:18 2:1,1 3:1	91:22 92:7	326:17	214:4 215:12
287:13,19,20	3:1 12:12	130:8 138:19	<b>eliminated</b>	<b>entering</b> 199:15
301:23 302:14	<b>E-G-L-I</b> 158:6	139:19 210:12	223:7,24	<b>entire</b> 10:21
303:19,20	<b>e-mail</b> 33:5,6,8	241:1 242:1	<b>ELLIS</b> 2:18 3:7	51:8,11 63:24
343:3 386:20	<b>e.g</b> 301:22	243:1 305:18	<b>ELMO</b> 18:15	64:2,5 75:2
387:1,6 388:14	<b>earlier</b> 22:18	305:19 316:2	22:8	180:17 181:2
388:17 389:22	23:24 24:10	342:11,16	<b>elongated</b>	207:4,6 218:1
390:9,19,20,22	27:14 28:14	396:5,15,16	364:22 371:19	228:21 230:4
390:23 391:6,8	31:1 71:5 76:8	406:1 407:7,13	<b>elucidated</b>	237:8 257:10
391:14,15	100:15 102:16	407:14 408:5	321:19	300:24 401:17
392:3,7,9,13	111:24 113:12	414:9,16 417:9	<b>embedded</b> 161:3	421:3
393:1 394:24	114:22 139:12	424:21,22	162:19 211:1	<b>entirely</b> 420:9
395:1	139:16 142:3	<b>effects</b> 17:10,15	<b>Embryology</b>	<b>entirety</b> 10:23
<b>draft</b> 6:10	182:8 210:9	18:19 19:3,8	218:6	163:20 176:7
104:24 105:9	214:15 219:3,5	19:18 23:14,18	<b>emergency</b>	207:22 230:20
105:16,21	220:18 226:15	24:1,6,15,18	12:19 383:22	309:5 353:2
201:17,23	235:10 240:20	25:7 138:20	384:1	<b>entitled</b> 72:19
346:12 347:4	240:23 270:24	250:24 252:7	<b>emphasis</b> 84:5	235:11 250:23
347:15 348:14	272:1 293:14	255:19 342:9	<b>emphasized</b>	301:9 306:23
349:4,7,16	298:7 300:5	343:20,23	76:11,16 84:4	<b>entity</b> 25:24
<b>drafted</b> 9:15	314:8 315:8	408:13 409:1	393:16	26:19 198:5



225:9	<b>Es</b> 158:5	<b>evaluated</b>	122:17,19	257:15,24
<b>environment</b>	<b>Escalator</b>	301:21	123:6,17 125:4	258:1 260:4,17
17:15 19:4,10	322:19	<b>evaluation</b>	127:24 128:3	260:22 263:6
19:21 24:3	<b>especially</b> 155:6	114:10 240:19	129:6 130:22	264:11,18,24
72:19 130:9	373:4	268:11,24	131:4 133:24	265:5,6,13,19
168:9 344:1	<b>ESQUIRE</b> 2:2,3	369:11,12	136:23 137:3,6	265:22 266:4
<b>enzyme</b> 395:4	2:8,13,19 3:2,7	399:5,12,14,17	139:4,11,13,22	267:8 268:14
395:11	3:12	401:10	139:23 142:9	268:15,17
<b>EPA</b> 357:22	<b>essence</b> 17:9	<b>evaluations</b>	142:16 144:2	269:11 270:6,7
358:11 359:22	414:5	342:1 400:9	147:1 149:24	270:9,11 271:2
371:11	<b>essentially</b> 26:15	401:7,11,21,21	150:1,15	271:13 272:11
<b>epidemiological</b>	268:2	401:24	151:11 155:19	274:8 276:4,10
208:22 255:3	<b>establish</b> 91:13	<b>event</b> 12:14	155:24 160:7	277:6 278:11
257:1 345:24	110:14 155:19	379:22	161:10 164:9	279:7 283:3
374:17 377:14	264:19 265:7	<b>events</b> 38:14	167:23 170:3	295:11 299:5
387:18,24	412:15	207:1 330:20	185:3 189:19	299:20 303:6
393:8 394:17	<b>established</b> 66:3	<b>eventually</b>	191:21,23	303:15,22
394:19 411:14	73:5 89:1	175:10 176:3	192:8 195:22	304:23 305:2
419:4 424:17	186:10 226:22	<b>everybody</b>	199:19 206:13	328:3 332:11
<b>epidemiologic...</b>	271:9 295:3	85:20 426:12	209:16,20,22	332:14,16,18
17:5	359:22	<b>evidence</b> 27:19	210:17,23	333:2,3,8,14
<b>epidemiologist</b>	<b>establishes</b>	28:23 29:10,11	212:22,24	333:17,23
301:21	110:9	29:18 30:8,10	214:6 215:4,9	337:12 343:13
<b>epidemiologists</b>	<b>establishing</b>	31:24 40:15	215:10 216:6	345:15,16
297:10 423:13	73:5 78:21	41:23 43:7	218:7,9 221:22	346:6 348:17
<b>epidemiology</b>	300:12 377:10	46:17 57:2,12	227:7,11	370:15 372:19
80:15,23 81:11	394:21	62:6,11,19,19	228:19 229:15	372:22 374:13
81:15,18,20,23	<b>establishment</b>	63:4,7,19 65:4	230:9,22	376:11 380:16
82:13,16 84:3	237:7	65:19 66:22	231:16,19,24	388:23 389:5
130:3 243:5	<b>estimate</b> 38:10	67:13,17,20	232:1,7 233:13	390:4 393:8
411:6,9 415:14	92:24	73:21 74:2,9	233:16,18	395:11,22
<b>epithelial</b>	<b>estimating</b>	75:22 76:9,15	235:24 236:2	405:15,20
228:13 293:21	146:22	76:21 77:6,10	236:12,16	417:18 418:15
326:20	<b>et</b> 5:20,22 6:2,4	77:16 78:2,10	237:22 238:1	418:15,16
<b>epithelium</b>	6:5,7,20 7:10	88:24 89:21	239:4,8,19	424:9
218:11,11,12	159:19 164:12	92:13 110:5,8	240:16,18	<b>evident</b> 403:9
253:10 328:5,5	166:15 170:13	110:9,13,18,23	241:10,17,22	412:21
402:23 403:8	172:8 174:16	111:2,7 112:12	241:23 243:5	<b>exact</b> 92:23
<b>equally</b> 387:24	190:6 202:24	112:13 113:4,4	244:10,13,20	97:20 114:16
388:7	206:13 207:3	113:8,24	246:10,11,23	122:14 226:16
<b>equivalently</b>	320:17 415:9	114:11 115:21	247:3,11,13,17	227:18 275:8
420:21 422:15	<b>etiological</b>	115:24 116:5,6	247:21,24	364:20 410:1
<b>errata</b> 4:10	164:20	117:16,21	248:5,9,11,15	<b>exactly</b> 32:21
433:6,9,11,15	<b>euphemistically</b>	118:24 119:1,7	248:15,16	38:4,6,8 71:7
434:1 435:7	282:18	119:13,17	254:2,9,12,13	93:22 118:14
<b>errors</b> 421:1,18	<b>European</b> 218:5	120:6,9,15	255:3 256:8,9	227:9
422:5	<b>evaluate</b> 378:22	121:8,15,22	256:20 257:1	<b>examination</b> 4:6

40:9 173:3,12 255:11 411:15 432:4 <b>examine</b> 62:5 84:13 162:17 237:6 274:22 <b>examined</b> 17:3 73:24 123:7 195:12,22 199:19 210:16 229:21 417:10 <b>examines</b> 171:7 <b>examining</b> 89:20 127:24 260:14 <b>example</b> 27:9 54:7 97:17 101:8,19 189:19 221:12 227:17,22 314:18 353:9 421:19 <b>examples</b> 16:24 <b>excellent</b> 65:17 <b>exception</b> 11:8 104:15 <b>excerpt</b> 5:8,12 5:18 20:2,7 26:20 81:22 82:2,12 141:9 180:24 <b>exclamation</b> 281:9 <b>excuse</b> 45:18 72:5 180:13 232:1 235:24 382:6 <b>exert</b> 91:22 <b>exerts</b> 396:15 <b>exhausted</b> 172:16 <b>exhaustive</b> 391:18 <b>exhibit</b> 9:6,11 9:12 10:16,23 12:3,9,12,22 13:20 14:2,13	17:17,23,23 19:14,23 20:1 20:6 22:7 26:7 26:8,21 45:24 49:19 50:1,3,8 69:15 72:9,10 72:15,17 81:24 82:1,8 83:8,17 93:7,7,8,11 94:8,10,11,12 101:7,7,13 102:18,19 104:11 106:24 141:6,7,8,14 142:23 157:17 157:18,19 158:19 159:17 159:18,23 160:2,2 162:2 164:5,11 165:7 166:13,14 167:21 168:6 170:11,12 172:6,7,20,23 174:14,15 175:15 179:21 180:23 181:10 182:9,22 183:11 190:10 190:11 194:8 194:21 196:19 197:4,5 201:10 201:16,21,22 217:10,14 219:6,6 220:5 220:8,14 223:13,16 224:16,17 225:2 235:8 249:9,10 250:19 252:8 256:7 261:9,12 261:20 272:10 273:10,11 274:6 276:3,20 278:10,14,23 280:1,2,9,22	282:6 284:15 284:19 293:5,6 301:19 320:16 320:22 326:8 327:7,21 328:21 329:2,7 329:12 340:13 340:13,14 346:14,17,22 347:23,23,24 348:21 351:11 351:12,22,23 351:23 352:19 353:13,13 356:12 357:3 357:15 359:12 362:11,12,24 369:6,10 386:11 398:15 398:16 399:22 405:13,19 408:20 410:10 415:7,8 416:2 419:9,10 <b>exhibits</b> 5:1 6:1 7:1 93:6 341:11 <b>exist</b> 282:12 <b>existence</b> 330:17 331:13 332:19 336:19 <b>exists</b> 55:16 168:9 226:12 <b>expect</b> 47:14 48:22 62:9 65:16 336:17 396:6 <b>expectation</b> 48:1 48:6 <b>expel</b> 323:6 <b>experience</b> 47:22 48:5,17 51:18 53:7 129:20 222:11 270:17 296:21 340:2 379:6 <b>experiment</b>	127:1 <b>experimental</b> 408:16 409:4 <b>experiments</b> 254:20 255:10 256:4 259:3 295:4 342:15 <b>expert</b> 5:4 6:18 9:7 14:24 21:21 104:3,14 109:3 120:5 229:19 250:3 264:24 284:20 285:1 297:14 336:9 370:4 411:5 427:19 <b>expertise</b> 34:3 45:19 49:12,14 52:19 81:19 130:16,17 131:6 132:11 133:11 138:14 138:15 212:14 267:24 270:4 270:24 295:16 296:14,15 297:21 315:13 339:24 340:3 365:18 <b>experts</b> 129:11 129:13,18 134:5,21,22 376:22 <b>expires</b> 432:22 435:17 <b>explain</b> 164:20 195:5 <b>explanation</b> 112:24 212:7 <b>exposed</b> 13:21 22:12 228:12 325:8 326:19 426:12 <b>exposure</b> 11:21 29:13,20 30:11 30:16,20 32:1 66:23 87:24	149:4 152:10 206:17 212:18 232:9 233:15 264:20 265:24 268:18 293:20 305:12 311:5 318:11 343:12 343:15,24 355:20 369:22 373:1,5 375:11 376:10 378:23 381:16 383:3 387:10 390:17 391:1,20 393:6 394:4 403:11 412:23 413:4,7 413:9 414:21 417:5 426:1,4 <b>exposures</b> 14:10 24:13 92:15 213:11 355:24 370:12 374:3 376:7 378:21 379:1 403:15 426:15 <b>extended</b> 280:7 <b>extensive</b> 292:21 334:15 403:10 412:22 413:8 413:11 <b>extent</b> 54:23 205:21 <b>exterior</b> 166:24 <b>external</b> 89:22 91:4 126:8 150:16 152:5 167:6,11,17 168:8 169:15 171:13 173:14 176:21 177:8 178:9 180:19 189:23 192:6 195:7,12,23 208:19 209:10 209:23 212:22 213:2,8 214:3 216:6 229:16
--	--	--	---	--

230:10 232:2,3 233:9,20,22 241:15 242:17 242:18 303:16 304:16,18 305:4 332:12 333:3 <b>externally</b> 215:11 244:18 260:18 <b>extraction-rep...</b> 162:16 <b>extrapolating</b> 407:1 <b>extrapolation</b> 405:18,23 406:18 407:5 408:3 410:13 410:16 <b>extrapolations</b> 406:13 <b>extremely</b> 408:2	65:11 67:5,10 69:8 70:8 71:21 77:14 78:17 85:13 89:6 90:14 95:11,18 100:24 101:1 102:13 105:14 105:20 116:22 120:2,18 121:9 125:18 129:3 149:2 154:9 171:21 175:21 185:16 187:17 188:2 196:6 198:1 204:12 205:17,22 207:9 213:16 217:7 219:9 227:22 243:21 248:12 278:17 278:18 299:13 301:9 308:19 310:14 313:17 319:8 330:16 331:10 338:11 350:4 396:5 425:1 <b>fairly</b> 243:17 <b>fairness</b> 85:9 <b>fall</b> 226:3 <b>fallopian</b> 175:9 176:3 182:18 183:7 184:14 190:1 228:9 253:10 326:16 <b>falls</b> 138:13,13 289:6 <b>familiar</b> 23:7 28:10 33:20 50:10,16,20 58:8 59:18 80:14 81:9 85:1,4,10,15 85:16 119:16 119:17 158:11 159:3,11 162:7	165:11 174:2 196:10 198:7 204:21 217:18 219:21 225:10 250:20 261:24 262:5,19 272:18 282:22 283:19 288:8 296:18,19 297:3 301:22 346:19 347:2,5 353:7 388:12 408:18 410:20 410:23 <b>familiarity</b> 34:12 35:5,8 35:10 420:10 <b>familiarize</b> 160:14 <b>families</b> 9:2 <b>far</b> 21:8 65:24 66:1 87:12 92:22 100:22 103:17 119:19 119:20 121:11 126:5 128:2 131:5 133:23 139:21 149:13 153:7,17 155:23 156:21 162:11 169:19 180:14 204:24 211:12 227:15 231:15 237:15 246:22 259:1 271:3 295:5 300:21 303:3 314:13 318:11 325:12 332:23 337:21 346:4 354:2 366:24 388:9 394:19 396:23 397:15 399:14 403:2 404:3 405:6 <b>fast</b> 161:22 <b>fault</b> 205:2	<b>fax</b> 1:23 6:11 217:15 <b>faxed</b> 262:23 <b>FDA</b> 6:13 17:1 224:18 225:11 225:20 230:1 232:12,15 234:5,7,20 235:6 236:6 237:20,21 238:4,14 239:20 326:8 327:4 328:13 329:6 366:20 376:18 <b>February</b> 342:6 <b>Federal</b> 50:14 50:17,20 <b>feel</b> 79:19 130:14 134:13 297:13 304:19 402:17 <b>feels</b> 134:3 <b>Fellow</b> 432:18 <b>felt</b> 342:11 <b>female</b> 89:24 91:6 108:14 109:6 110:11 111:9,23 116:9 120:12 135:21 137:14 152:17 167:17 168:10 195:24 213:22 215:13 232:4 260:19 303:17 327:13 <b>fence</b> 247:17 248:10 258:10 258:11,12,20 <b>fertility</b> 171:2 <b>fiber</b> 364:24 <b>fibers</b> 14:20 327:16 <b>fibrosis</b> 400:12 402:3 <b>fibrous</b> 364:18 364:22 365:1	365:16,22 366:7,9 371:14 <b>field</b> 20:22 97:20 129:24 <b>fields</b> 130:2,5 <b>fifth</b> 13:4 <b>figure</b> 131:17,18 131:21 260:7 334:7 337:2 <b>file</b> 95:6 100:3 <b>final</b> 83:3,16 289:21 290:4 290:20 <b>financially</b> 432:15 <b>find</b> 61:16 65:9 66:4 107:19 108:21 113:23 147:5 175:12 187:24 221:12 236:1 251:24 306:21 346:21 350:11 351:17 354:5 375:24 392:11 <b>finding</b> 234:7 256:3 400:14 400:18 403:8 <b>findings</b> 152:15 153:4 281:12 367:19 368:15 <b>finds</b> 221:21 235:23 <b>fine</b> 11:5 125:18 143:19 188:12 205:2 299:15 431:12,14 <b>finish</b> 236:23 323:19 <b>finished</b> 237:2 399:16 <b>first</b> 13:1 14:2 14:13 20:8 22:7 32:16,19 34:10 36:12 50:10 61:8 74:22 77:3
<b>F</b>				
<b>F</b> 3:13 <b>facility</b> 14:11 <b>fact</b> 85:12 117:7 117:14 123:16 237:19 277:7 308:9 320:24 352:21 378:14 379:6 405:24 406:22 407:6 426:11 <b>factor</b> 337:6 <b>factors</b> 84:8 155:8 163:23 313:3 <b>factually</b> 279:9 <b>fail</b> 115:24 433:18 <b>fails</b> 114:12 <b>fair</b> 9:23 10:1,4 10:9 27:16 35:1,11,22 38:9 43:24 44:8 61:6 64:1				

82:7 96:5	<b>focused</b> 16:17	98:10 100:18	331:12 334:11	68:10 74:5
109:2 122:2	155:10 161:19	<b>formed</b> 112:5	387:13,16	77:20,24 78:18
124:14 125:20	<b>focusing</b> 18:16	113:9 193:22	<b>four</b> 5:5 12:4	79:2,14 80:24
125:21 135:11	<b>folder</b> 284:17	264:23	13:9,15 125:9	84:16 88:22
135:17 136:7	<b>folks</b> 61:17,23	<b>formidable</b>	137:23 185:22	89:15 90:16
152:7 162:23	96:13 273:5	253:8 259:15	251:14,19,22	91:18 92:2,11
164:6,18,22	<b>follicle</b> 171:2	<b>forming</b> 133:5	252:9	93:19 94:7,12
168:6,12	<b>follow</b> 134:14	135:5 175:1	<b>fourth</b> 13:8	94:17 103:10
170:20 182:4	151:17 154:3	254:14 255:6	125:20 350:12	104:22 107:5
187:9 188:14	253:2	266:5	<b>fragments</b>	108:17 109:1
217:22 252:4	<b>followed</b> 312:24	<b>formula</b> 218:14	371:19	112:9 113:1
282:4 293:16	313:21 321:13	222:20	<b>fragrances</b>	114:14 117:9
294:15 307:3	321:14 325:10	<b>fornix</b> 158:22	216:18	118:13 119:15
307:19 308:3	<b>following</b> 27:16	159:8	<b>fragrant</b> 338:18	120:7 121:24
308:13,21	127:18 136:12	<b>Fort</b> 1:15,16 8:9	<b>frame</b> 254:10	122:8,21 123:9
309:10 351:21	164:10 179:3	18:12	<b>framework</b> 7:3	123:21,24
383:10 399:4	179:23 333:10	<b>forth</b> 42:2 56:6	348:2,6 349:10	126:16,22
401:6 408:12	<b>follows</b> 8:19	56:23 59:11	<b>FRCP</b> 432:10	127:21 128:13
408:24 420:14	<b>food</b> 169:22	64:12 78:8	<b>frequency</b> 92:15	129:22 130:18
<b>Fiume</b> 291:22	225:3,6,11,13	101:15 146:1	<b>frequently</b>	132:3 133:14
<b>five</b> 402:9	226:3	184:13 203:23	388:11	134:7,11,16,24
<b>fix</b> 205:3	<b>footnote</b> 350:13	247:23 354:19	<b>front</b> 61:2 156:9	138:16 139:9
<b>fixing</b> 131:19	<b>foregoing</b> 432:7	432:8	177:15 178:18	140:6,15,24
<b>flag</b> 283:1	435:4	<b>forward</b> 139:11	191:2 208:16	145:23 153:15
<b>flawed</b> 107:17	<b>foreign</b> 107:16	200:16 227:11	214:14 244:6	155:1 156:16
108:3,8 109:15	137:17 138:3	229:12,19	324:10 360:14	166:10 167:12
109:23 186:6	140:5 163:5	267:2,15 268:5	364:20 399:9	168:20 169:21
186:11,14,16	228:10 310:18	270:13 370:4	402:20 409:6	171:16 172:1
186:17 303:8	311:17 312:15	428:18	<b>Frost</b> 3:2 10:11	173:8 174:7
<b>flip</b> 252:20	312:19,21	<b>found</b> 50:2	10:19 11:2	175:18 177:23
<b>flipping</b> 203:10	313:5,20 316:4	64:17 65:13	15:13 16:4,20	179:5,9 180:7
<b>Floor</b> 2:20	316:6,22 317:1	70:23 113:18	19:15 21:6	182:23 185:17
<b>Florham</b> 3:4	317:6,12,15,18	114:6 117:4,16	24:20 25:12	186:7 187:1
<b>flow</b> 11:3 135:20	318:3 319:7	131:3 158:23	28:18 29:8,21	188:20 189:9
136:8,10 137:8	321:7 323:6,16	161:2,3,15	30:6 31:12,21	190:16 191:16
137:13	325:9,15 326:4	162:19 182:16	32:20 40:18	192:18 193:11
<b>Flower</b> 2:20	326:17 327:2,5	183:16 184:21	41:18 42:8	193:24 194:13
<b>fluids</b> 135:21	328:9 330:19	187:16 193:5	43:2,13 44:17	195:1 196:22
136:9,11 137:8	<b>form</b> 16:9 51:6	194:6,20,21	45:17 46:14	199:9,21
137:13,14	145:16 146:9	209:1,17	47:9,18 48:11	200:10 204:18
<b>FLW</b> 1:5	199:21 215:4	210:15 211:1	49:5 51:6,23	205:9 208:3
<b>foam</b> 14:17,19	290:20 370:9	215:5 231:24	52:8 53:5,23	209:3,18
15:4	373:24 435:6	261:7 332:14	54:22 57:8	210:18 211:2
<b>focus</b> 31:8,17	<b>formal</b> 40:19	342:10 355:18	58:21 60:1,24	211:23 212:9
85:18 86:19	<b>formally</b> 40:7	369:22 372:24	61:19 62:2,14	214:11 215:1,7
132:23 136:7	98:7	378:20	64:4 65:1,22	219:10 220:11
383:10 401:4	<b>formatting</b>	<b>foundation</b>	66:9,19 67:23	220:17 221:13

221:24 222:22	332:21 333:11	427:18,22	<b>generalities</b>	114:9 116:8
224:6 225:16	334:5,13 335:7	428:6,24 429:6	119:4 121:13	168:10 175:8
226:5,18 229:3	335:12,15,23	429:19 430:3	122:23 156:18	176:2 186:1
230:2,17	336:4,22 337:8	430:11,19,21	385:7	250:12 260:2
232:18 233:6	338:2 339:8,16	431:8,11,17	<b>generally</b> 13:11	345:3
234:11,23	340:1 341:1,5	<b>full</b> 18:16	13:13 20:21	<b>genitalia</b> 167:1
236:7,23 238:6	341:7 342:18	223:18 226:11	31:4 59:14,21	167:17 171:13
239:16 240:21	343:6 344:6	243:19 263:4	101:13 118:6	173:15 176:22
242:3,7 243:12	345:6,10,21	<b>fully</b> 136:6	127:9 137:21	<b>genitals</b> 242:19
245:17 246:14	347:16 348:18	<b>function</b> 170:23	140:16 144:24	<b>genre</b> 328:6
247:6 248:3,13	349:6,22 350:5	389:24 390:4	153:1 158:12	<b>geologist</b> 292:22
250:13 251:5	351:8 354:11	<b>fundamental</b>	159:12,14	366:3
254:4 255:17	356:6,15 357:5	56:14	166:23 171:23	<b>geology</b> 292:19
256:10 258:3	357:17 358:13	<b>funny</b> 28:8	181:24 195:21	292:21
258:13,19	359:14 360:8	<b>further</b> 124:5	249:17 257:3	<b>GEREL</b> 2:13
259:8,21 260:9	360:17,23	163:15 164:1	285:7 294:9	<b>German</b> 281:1
263:11,22	361:3,8,12,21	432:6,10,12	296:7 298:23	<b>getting</b> 21:13
264:16 265:3	363:6,13,20	<b>future</b> 362:17	304:15 305:11	146:15 260:8
265:16 266:7	365:4,17 367:7		316:9,21	280:6 297:24
266:11,18	367:21 368:17	<b>G</b>	319:24 320:1	318:6,24
267:11 268:10	370:9,23 371:5	<b>G.E</b> 158:6	326:3 329:18	339:17,23
269:4,14,23	371:8 372:4,12	<b>gather</b> 64:23	336:5 337:20	424:3
270:22 271:20	373:9,24 375:6	65:2 118:22	343:21 365:5	<b>give</b> 92:23 96:23
271:23 272:15	375:15,19	120:17 121:6	383:22 384:10	160:14 200:7
273:18 274:16	376:2,16 377:4	285:23	385:13 420:12	208:1 217:23
275:19 276:5	377:8 378:2,10	<b>gathered</b> 67:21	<b>generate</b> 63:6	258:8 284:17
276:21 277:4	378:18 379:10	191:21 265:11	131:14 285:10	351:5 375:2
278:2,21	380:8,14 381:9	265:13 312:8	286:1 288:1	415:6
280:13 283:4	381:23 382:4	<b>gathering</b> 63:19	324:1	<b>given</b> 65:15
286:7 288:4	382:23 383:12	64:21 121:21	<b>generated</b>	121:14 176:5
290:8 291:7,21	384:9 387:14	164:10 267:7	137:15	177:15 184:9
296:3,17	388:1 389:1,6	<b>general</b> 21:9	<b>generates</b>	227:19 330:15
297:15,18	390:14 391:10	38:23 40:8,21	385:12	361:14 362:24
298:18 299:7	392:15 393:18	41:8 42:2 43:5	<b>generating</b>	435:5
299:22 301:10	393:21 395:13	43:18 44:6	291:15	<b>giving</b> 193:12
303:10 306:1	395:23 396:21	50:21 53:11	<b>generation</b>	379:12
306:11 307:17	397:23 398:10	117:20 119:21	54:15 120:4	<b>glad</b> 74:20
308:2,11,20	400:2 406:10	121:5 154:10	287:2 324:1	223:15 346:16
310:21 311:9	407:10,23	154:11,23	<b>generic</b> 70:14	<b>glance</b> 11:6
313:23 315:14	410:11,22	155:10,15,21	<b>genetic</b> 306:17	169:5
316:7 317:8	412:7 413:2,13	156:15 199:23	307:22 320:11	<b>Global</b> 7:4 54:16
318:1,5 319:9	414:14,18	225:24 244:23	334:15 335:3	54:18 56:5,23
323:9 324:16	416:20 418:23	300:18 314:12	346:4 418:4	351:13 354:14
325:6 327:9	421:8,21,24	325:22 330:6	<b>genital</b> 89:3,10	358:1,3 359:24
328:11 329:3	422:24 425:9	338:6 343:3	89:23 108:5	362:7 371:10
329:13 330:22	425:19,21	346:16 364:21	111:9,17	<b>Globally</b> 353:3
331:2,16 332:3	426:22 427:8	390:6 408:4	112:16 113:21	<b>gloves</b> 173:3



<b>go</b> 13:22 26:6 35:19 36:22 49:23 55:2 59:10 74:8 79:20 82:21 84:24 86:4,7 87:20 94:22 103:20 114:19 118:14 130:13 133:4 135:3,15 143:3 146:8,16 148:1 149:1 151:8,14 152:14 154:13 158:1,5 163:15 176:9 178:4 180:23 181:21 182:2 187:23 189:12 190:24 197:24 202:21 206:23 219:19 237:1 251:11 257:13 258:18 280:18 290:17 301:3 311:19 316:4 320:3 321:24 326:7 326:12 331:8 338:3 347:8 349:8,13 351:9 354:14 359:21 363:23 367:8 368:18 372:15 385:16 386:18 405:13 409:18 416:11 <b>goal</b> 41:20 43:15 43:15 390:15 <b>goes</b> 75:19 149:21,21 180:11 203:6 228:17 255:2 274:17 279:12 281:6 291:14 322:12 342:5 <b>going</b> 10:7 13:4 13:5 18:15	22:21 26:4 85:19,24 86:8 86:20 93:19 94:17,23 131:18,19 146:16,18 147:14 157:16 158:1,16 160:17,17 162:1 163:1 191:23 201:22 206:22 218:24 226:10 228:3 240:5 243:16 273:19 280:16 283:24 284:17 290:9,21 293:4 297:8 298:10 301:4 309:13 309:13,15 311:22 320:5 326:9,12 346:18 351:1,5 354:6 362:16 362:18 364:7 364:19 373:18 388:19,20 398:14 402:21 404:11,23 408:20 424:24 427:14 430:23 431:11,21 <b>Golkow</b> 1:23 3:21 8:5 <b>good</b> 8:21,22 9:16 10:5 11:10,23 32:23 34:21 52:2 53:3,10,14 77:22 87:20 94:14,20 124:6 147:21,24 161:10 195:4 224:4 361:10 396:19 419:20 <b>Goodman</b> 84:9 <b>Goodness</b> 42:19	339:6 429:18 <b>Google</b> 39:1,8 64:7 252:1 <b>government</b> 151:7 201:1 208:5 238:15 <b>governmental</b> 200:20 201:6 235:11,18 238:8,16 239:21,24 <b>grade</b> 291:1 <b>grades</b> 290:19 <b>Gradient</b> 203:17 <b>gravity</b> 117:6,7 117:12,13 123:5,12 124:17,20,23 125:3,21,22,24 126:3,20 127:5 127:6,17 128:1 128:5,11,14,18 129:2,4 135:14 135:20 136:14 136:19 <b>great</b> 137:12 290:17 337:18 338:16 <b>greater</b> 88:8 103:23 227:15 298:8 376:23 <b>Greenland</b> 81:4 85:11 <b>group</b> 100:21 147:1 162:21 185:3 283:7 355:22 <b>growth</b> 400:11 402:2,15 <b>guarantee</b> 64:16 <b>guess</b> 15:3 111:11 122:12 144:17,17,18 269:16 286:8 288:24 297:19 302:18 356:11 399:6,12 420:8	<b>guidance</b> 224:5 <b>guide</b> 5:7 17:18 280:24 <b>guidelines</b> 53:8 56:7,23 57:23 58:12,24 60:8 354:17 356:17 356:21 357:7,9 357:22 358:4 360:2 362:4 371:11 <b>gumbo</b> 271:15 <b>guys</b> 340:23 <b>gynecological</b> 148:13 164:21 173:2,12 <b>gynecologist</b> 131:8 <hr/> <b>H</b> <hr/> <b>H-E-L-L-E-R</b> 206:13 <b>H-U-N-C-H-A...</b> 301:23 <b>half</b> 307:19 308:3,13,21 309:10 <b>halfway</b> 107:21 <b>hand</b> 301:6 <b>handed</b> 189:11 <b>handful</b> 188:7 189:11 <b>handing</b> 9:10 <b>handwritten</b> 6:16 273:12,20 277:16,21 278:5 <b>happen</b> 82:9 97:6 <b>happens</b> 334:4 <b>happy</b> 133:17 138:7 178:5 179:15 <b>hard</b> 65:9,13 295:19 <b>hard-and-fast</b> 75:22 76:15	<b>harmful</b> 22:11 25:1 46:3,12 173:5 <b>Harmonization</b> 54:16,18 56:6 56:24 354:15 358:1,3 359:24 362:7 371:10 <b>Harmonized</b> 7:4 351:13 353:4 <b>hazard</b> 49:4 51:3 55:16 56:3,24 57:17 58:2,5,9,14,20 59:7,13,16,24 60:23 257:18 355:3,3,9 356:20 357:10 360:4 <b>hazards</b> 48:9 51:21 52:4 56:5,16 57:6 430:8 <b>head</b> 73:12 80:12 97:7 144:14 250:21 260:7 341:22 429:22 <b>header</b> 262:10 <b>heading</b> 108:1 187:10 197:19 252:23 405:17 <b>health</b> 6:10 7:2 19:3,8 51:3 97:11,16 104:24 105:9 105:10,16,21 106:2 138:20 139:18 201:17 201:24 202:9 202:17,18 204:15,21,24 206:7 207:15 208:2 210:12 225:5 241:1 242:1 243:1 257:18 305:18
--	--	---	---	--

305:19 343:23 346:9,20 347:3 347:15 348:1 348:13,23 349:3 354:18 364:23 414:9 <b>healthy</b> 317:10 <b>hear</b> 19:11 70:9 247:20 257:21 266:3 273:4 299:11 333:20 373:13 400:23 <b>heard</b> 42:16 43:23 81:3,6 130:11 241:19 268:21 385:19 <b>hearing</b> 201:11 377:22,23 <b>heavy</b> 285:13 287:22 289:20 292:11 355:19 355:23 374:2 375:22 378:20 423:22,23,24 424:5,8,11,15 424:19,23 425:8 <b>heightened</b> 417:4 <b>held</b> 1:15 <b>Heller</b> 206:12 208:11,15 210:1 211:21 212:2 <b>help</b> 30:4 38:15 93:24 98:11 108:21 123:21 124:7 147:5 195:4 212:8 279:1 397:1 399:19 404:22 405:6 <b>helped</b> 328:20 328:24 <b>helpful</b> 192:17 <b>helps</b> 63:11 220:5 386:7	<b>Henderson</b> 5:20 6:2 159:19,24 160:3 162:15 166:15 167:21 168:5 176:14 190:6,9,12 191:12 193:5 193:13,16 194:5,7,19,20 195:19 196:4,8 196:18,19 <b>hereinbefore</b> 432:8 <b>high</b> 369:22 370:12 372:24 <b>highest</b> 289:20 <b>highlighted</b> 147:4 160:24 162:2 175:13 217:22 341:8 <b>highlighting</b> 340:19,21,22 341:2 <b>HIGHTOWER</b> 2:3 <b>Hill</b> 5:11 27:1,5 27:13,21 28:1 28:4,15,20 29:16,24 72:2 72:5,5,11,18 73:3,9,10,17 73:18,22 74:16 75:19 76:12 77:15 78:9,24 79:5 80:3 82:19,24 83:12 84:3,15 85:3 86:22 87:6 113:18 114:23 115:12 116:1 203:7,7,8,20 203:23 204:11 207:12 211:12 212:20 223:5 227:1 233:12 236:16 237:4 243:4 259:12	259:18 300:3,7 305:7,10 333:14 419:5 <b>Hill's</b> 85:3 112:20 <b>Hilton</b> 1:15 <b>hires</b> 47:20 49:7 <b>historical</b> 290:24 <b>history</b> 178:18 <b>Hmm</b> 404:13 <b>Holmes</b> 223:6 223:23 <b>Holmes/Watson</b> 259:18 <b>home</b> 18:6,11 131:15 420:2 <b>homeostatic</b> 400:11 402:2 402:15 <b>Hopkins</b> 261:10 261:11,15,17 <b>hospital-based</b> 418:2 <b>hour</b> 101:16 102:2,6 351:2 <b>hourly</b> 101:15 276:15 <b>hours</b> 92:21 93:1 96:6 101:8 275:5,10 275:17 276:14 379:4 <b>Howe</b> 13:7 <b>Hudson</b> 13:5 14:12,14,16 <b>Hugh</b> 86:20,21 <b>Huh-uh</b> 249:7 <b>human</b> 17:16 140:18 141:3 174:1 218:4,5 225:5 317:11 355:14 387:18 388:5 393:9,14 395:20 396:16 397:4,5,5,16 397:19 409:23	<b>human-based</b> 394:20 <b>humans</b> 173:2 396:4,6,13,20 405:19 406:18 406:21 407:2 407:14 408:6 408:15 409:3 409:21,24 410:3,14,18 411:17 <b>Huncharek</b> 301:23 302:6 302:14 <b>hundreds</b> 275:17 <b>hung</b> 309:14 <b>hygiene</b> 14:9 250:9 <b>hygienic</b> 249:18 249:21 250:6,6 252:23 257:1 <b>hyperplasia</b> 402:22,23,24 403:8,22 404:4 412:20 <b>hyperplasias</b> 414:21,22 <b>hypotheses</b> 256:21 303:22 <b>hypothesis</b> 74:11 88:15 89:8,21 111:21 112:13 113:19 118:17 120:9 126:7 128:4 137:4 213:18 214:2 216:7 218:8 221:23 233:19 236:13 241:14,18 244:17,20 303:15 398:12 <b>hypothesized</b> 118:12 206:9 <b>hypothetic</b> 261:2	<b>hypothetical</b> 177:10 377:16 381:4 <b>hypothetically</b> 381:18 <hr/> <b>I</b> <hr/> <b>IARC</b> 5:18 7:6 141:9 142:8,21 143:1,7,11 144:8,12,21 145:10,13,15 145:20,21 146:2,6 150:4 150:23 151:6 153:8,21 180:24 181:14 182:4 184:13 186:23 187:5,8 187:15 188:1,9 188:16,17,23 189:2,5 190:6 195:10 200:24 355:13,18 362:13 363:3 369:5,17,22 370:2,3,11 372:23 374:1,7 375:9 378:20 <b>idea</b> 89:6 111:3 119:13 125:3 423:12 <b>identical</b> 83:17 396:12 397:19 406:21 410:18 <b>identification</b> 9:8 12:6 17:20 20:4 26:10 50:5 72:12 82:4 93:10,13 102:22 141:11 157:22 159:21 164:14 166:17 170:15 172:10 174:18 197:8 201:19 217:17 224:19 249:12
---	--	---	--	---

261:14 273:13	<b>importance</b> 84:7	170:17 172:18	342:14	312:24 313:6
280:4 284:22	<b>important</b> 91:16	174:5,23	<b>independent</b>	313:22 315:16
293:8 320:19	132:13 139:8	181:15 200:5	25:17 145:16	315:18 317:9
340:16 348:3	220:9 235:20	202:18 205:21	264:24 266:9	317:19 319:4,8
351:16 355:9	240:17 254:1	254:18 286:15	<b>independently</b>	319:20 320:6
357:11 362:14	299:4 354:22	287:4,4,7,8	144:19 145:14	320:10 321:13
386:14 398:19	<b>impossible</b>	309:20 310:7	189:6 281:4	321:15 325:11
415:11 419:13	113:13 163:11	356:3 357:8	<b>INDEX</b> 4:1	328:5,10 329:8
<b>identifications</b>	223:7 224:1	360:3 365:11	<b>indicate</b> 210:10	330:11,19
355:4	259:19	367:5 368:15	210:11 238:24	334:16,17,24
<b>identified</b> 69:5	<b>impression</b> 43:6	374:20,22	257:16	335:10,21
69:17,23 70:12	<b>improbable</b>	377:18 423:24	<b>indicates</b> 158:20	336:12 337:11
193:10 207:3	223:8 224:2	<b>includes</b> 19:20	<b>indisputable</b>	337:17 338:1,5
210:4 212:6	259:19	22:5 24:5,17	73:21 74:2,9	338:16,20,22
351:11	<b>in-depth</b> 206:3	26:17 76:20	76:9,21 77:6	339:2,3 340:3
<b>identify</b> 9:12	<b>inaccessible</b>	93:2 115:17	77:10,15 78:2	340:4 346:5
51:20 52:4	105:17	141:22 167:6	78:10 228:6	400:12 402:3
56:1 57:6	<b>inaccurate</b>	167:10 270:16	229:1 253:5	<b>inflammatory</b>
71:16 93:16	79:16 282:17	301:19 305:7,8	260:4	228:11 313:6,9
292:8,13	344:14	343:19 353:14	<b>indistinguishable...</b>	313:13 314:2,5
386:24	<b>inanimate</b> 253:6	357:15 360:14	161:11	316:13 317:2
<b>ignore</b> 236:5	259:13	379:21 420:22	<b>individual</b> 13:23	318:9,12
<b>ignored</b> 237:23	<b>inappropriate</b>	422:16	52:13 119:21	319:15 323:24
239:13	98:14	<b>including</b> 19:10	150:11,17	324:3 325:17
<b>II</b> 201:3	<b>include</b> 28:5	23:16 47:8,16	153:2,9,22	325:22 326:18
<b>images</b> 161:6	36:4 52:3	48:8 49:2,15	154:5 209:8	327:3,6,18
<b>imagine</b> 253:6	101:2 115:12	130:2 167:18	239:24 272:6	328:21 329:19
259:13	167:4 191:14	167:19 307:8	314:6 368:19	330:2 334:20
<b>Imerys</b> 216:10	193:8 216:23	344:1 355:7	412:1,13,16	335:2 340:6
216:11,24	235:16 269:2	374:21 380:5	<b>individuals</b> 95:9	389:9
217:6 285:8	286:4 356:12	392:13	153:3 417:11	<b>information</b> 6:9
290:10 366:24	359:12 365:15	<b>inclusion</b> 127:17	<b>induce</b> 317:19	11:13 14:23
<b>immediately</b>	367:18 374:19	128:11 129:2	<b>industrial</b> 14:9	54:1 56:9
71:10	381:3,17	<b>inconclusive</b>	<b>industry</b> 54:9	62:12 63:10,14
<b>immune</b> 389:24	382:14 389:18	279:18	<b>inert</b> 158:21	64:24 97:3
390:3	389:24 411:22	<b>inconsistent</b>	159:4 182:16	139:20 177:5
<b>impact</b> 169:19	412:5 415:3	257:4 279:18	183:5 189:21	184:8 197:7
295:11	424:9,18 425:4	<b>incorrect</b> 279:9	<b>infant</b> 430:2	199:1,24
<b>impacts</b> 295:7	<b>included</b> 10:20	<b>increase</b> 199:12	<b>inference</b> 84:12	231:13 235:20
396:12	14:19 18:1	414:4	<b>inferences</b> 84:4	237:16 246:16
<b>impairment</b>	48:9 69:14	<b>increased</b> 257:2	<b>inflammation</b>	246:22 247:8
400:10 402:1	83:4,18 106:10	404:5,8 414:2	206:11 218:12	248:5,9 260:12
<b>imperative</b>	106:12 117:1	414:2	306:23 307:9,9	260:13 264:7
433:14	128:20 129:4	<b>increases</b> 414:5	308:5,15	265:11,12
<b>implications</b>	133:18 154:14	<b>incriminate</b>	309:20 310:8	274:21 275:2
133:22	161:7 164:7	163:11	310:11,12	275:16 287:3
<b>implies</b> 176:20	167:22 168:14	<b>incubation</b>	311:4,6,11,14	289:3,4 324:20

328:15 335:16	<b>inside</b> 126:14	<b>interpret</b> 52:24	211:9 215:16	118:3 121:8
342:20 343:9	248:10 258:11	<b>interpretation</b>	271:1 292:1	153:7 154:19
354:3 355:1	<b>insofar</b> 365:10	156:7	300:23 313:12	216:22 244:4
396:8,18,23	<b>instance</b> 27:12	<b>interrupt</b> 11:3	313:15,16	304:2 312:1
397:5,17	70:22 426:9	35:22,24	314:2,6 318:12	319:5 334:2
403:16 406:17	<b>instances</b> 12:11	<b>interrupting</b>	325:19 330:5	365:2 403:12
408:4 410:4,16	317:18	94:22	336:7 380:19	426:9
411:23 412:5	<b>Institute</b> 197:17	<b>interval</b> 420:21	384:3,13	<b>italicized</b> 25:10
412:15 426:14	198:6,8,11	422:16	<b>involves</b> 49:14	76:17
<b>ingredient</b>	199:8 200:9	<b>intervals</b> 296:20	167:16 316:20	<b>italics</b> 23:13
356:18 357:8	<b>INSTRUCTL...</b>	<b>interviewed</b>	330:19	<b>item</b> 54:8 55:17
358:5 360:3	433:1	416:15 417:11	<b>involving</b> 14:24	104:15 197:11
362:8	<b>insufficient</b>	417:12	166:21 316:23	199:6
<b>ingredients</b>	91:13 282:13	<b>intricate</b> 319:14	332:19 334:3	<b>itemized</b> 96:21
36:24 37:9,11	<b>insulation</b> 14:17	320:11	384:7	102:5
271:16,22	15:4 375:24	<b>introduction</b>	<b>irradiation</b> 311:19	<b>items</b> 49:24
428:19	<b>intact</b> 170:23,24	137:16 168:7	<b>irritant</b> 325:1	68:22 104:10
<b>inhalation</b>	<b>intend</b> 9:22	168:14,22	<b>irritation</b>	205:21
107:15 109:8	429:12	169:13	206:10 310:20	<b>iteration</b> 23:23
311:24 312:2,8	<b>intended</b> 64:1	<b>investigation</b>	311:8,11,13	
312:10,10	257:17 344:18	214:8 221:11	312:17,22,24	<b>J</b>
382:20 430:8	344:21 345:4	304:13	313:21 317:2	<b>J</b> 219:8
<b>inhalational</b>	<b>intent</b> 63:21	<b>investigations</b>	321:10,13	<b>J&amp;J</b> 27:15 28:2
403:15 414:21	277:20	163:16 164:2	325:10 338:19	28:17 92:21
<b>inherent</b> 294:11	<b>intention</b> 63:18	<b>investigators</b>	<b>issue</b> 13:11	229:24 281:21
<b>inhibited</b> 395:3	64:23	281:4 305:22	14:14 27:2	285:8 290:10
395:21	<b>intentional</b>	306:7 307:5,14	32:11 33:15	366:24
<b>initial</b> 55:15,23	245:19 246:3	309:16 310:4	37:19 53:22	<b>JACK</b> 3:2
310:19 311:7	<b>intents</b> 287:20	310:16	54:21 55:3	<b>jack.frost@db...</b>
311:19 312:16	374:8	<b>invoice</b> 94:6,9	65:10 89:5	3:3
321:10,12	<b>interest</b> 39:18	96:21 101:18	92:19 107:10	<b>Jersey</b> 1:1 3:4
335:21	40:4 41:3,9	155:13	112:18 116:12	<b>Jessica</b> 32:21
<b>initiate</b> 305:23	43:4,18 44:10	<b>invoices</b> 94:24	120:6,17 123:7	<b>JNJ</b> 249:14
306:9 307:7,15	44:20 45:6	96:2	131:23 132:2	<b>JNJ_000704</b>
309:18 310:5	162:22 281:13	<b>involve</b> 12:22	133:9 134:22	217:11
<b>initiates</b> 218:11	<b>interested</b> 41:5	13:10 14:3	144:20 149:17	<b>job</b> 96:24
328:5	160:18 400:6	183:5 312:8	196:5 243:10	<b>John</b> 261:10,10
<b>initiation</b> 307:10	432:15	316:2	246:8 275:18	261:15,16
310:13 334:18	<b>interim</b> 399:5,11	<b>involved</b> 13:15	276:16 299:5	<b>Johnson</b> 1:3,3
335:18 336:7,8	399:14,17,19	13:16 14:8,16	301:22 304:9	2:22,22 3:5,5
336:14	400:8 401:6,9	16:10 24:14	304:21 305:6	9:3,4 11:12,12
<b>injecting</b> 267:21	401:11,24	25:6 31:4	312:10 318:11	11:14,15 15:12
270:20	<b>interlibrary</b>	32:14 54:3	373:19 376:14	15:12,21,21
<b>input</b> 55:7	63:12	127:12 129:13	377:3,7 379:5	16:1,1,18,18
<b>inserted</b> 352:15	<b>internal</b> 221:14	131:9 132:22	408:21	17:1,2 31:2,3
<b>insertion</b> 195:16	<b>International</b>	137:19 153:8	<b>issues</b> 52:19	31:11,11,18,19
214:16	141:20	153:20,24	98:10 100:17	31:20,20 32:6

32:7,13,13,18	428:16,16	210:8 225:24	131:6 132:5,11	225:19 226:1,6
32:18 33:1,1	430:9	259:11 260:6	132:23 133:21	227:13,18
33:12,12,17,17	<b>Johnson's</b> 36:14	285:10 295:1,2	135:12 136:22	230:19 231:7
34:6,6,11,11	42:7 67:6	295:13,18,20	137:11,22	231:14,14
34:13,13,14,15	226:2 367:2	296:8 311:12	138:4,18	234:15,24
34:23,23 35:13	376:19 382:9	315:2	140:13 144:11	236:19 237:11
35:13,15,15,17	430:1,9,9	<b>kinds</b> 407:1	144:17 145:1	238:9 239:23
35:17 36:1,1,6	<b>joined</b> 385:18	<b>Kissler</b> 6:4	146:8 147:6	240:1 241:11
36:6,14,21,21	<b>journal</b> 173:21	170:11,13	149:23 150:11	242:22 244:23
42:6,12,12	218:3,4 221:4	<b>knew</b> 42:13	150:11 151:1,7	245:7 248:20
46:22,22,24	419:17,19	259:6 373:17	151:13,18	249:20,23
47:1,11,11,14	420:12	373:19 376:13	152:23 153:6,7	250:17 251:2,6
47:15,20,20	<b>journals</b> 303:1,3	<b>know</b> 24:7,21	153:13,23	251:8,21,23
48:7,7,23,23	<b>JR</b> 2:2 3:2	28:12 30:3	155:3 156:6,8	252:2,15 255:2
49:7,7 53:4,4	<b>judging</b> 178:17	31:16 32:10	157:10 159:7	256:2,3,23
53:19,19 61:11	262:16 401:13	33:18,21,22	159:10 160:12	258:9,10 259:9
61:11,12,12,13	<b>jump</b> 98:16	34:5,14,16	165:12 168:15	260:13,23
61:13,17,17,23	<b>jumped</b> 311:11	35:12 37:10	168:16,23	261:10,15,16
61:24 62:4,4	421:9	38:3,6,17	169:1,3,12	261:23 262:6
62:10,10,24,24	<b>jumping</b> 238:17	39:16,19,20	170:4,4 171:15	262:14 263:13
65:17,17,23,24	283:11	40:2,5 41:19	171:18,24	263:23 268:4
66:6,7,13,13	<b>jurisdiction</b>	41:21 42:1,10	172:2 176:22	269:5 272:1,17
66:17,17 67:2	225:14	45:20 46:21,24	179:18 180:17	272:18,23
67:2,6,7,7,13		47:10,19 48:2	182:13 183:2,3	274:15,22,24
67:13,20,20	<b>K</b>	49:6 50:9	184:9,15	275:5,8,22
68:2,2,6,6,12	<b>K-I-S-S-L-E-R</b>	52:14,21 53:9	185:21 186:19	276:24 277:6
68:12 95:1,2,3	170:11	53:11 55:9,10	188:14 189:17	277:10,15,22
95:3,6,7,15,15	<b>keep</b> 85:24	56:16 57:21,23	191:5,18	278:6 282:20
95:17,18 96:14	126:21 141:15	64:6,16 65:3,3	193:16,16,18	282:24 283:12
96:14 99:23,23	181:3 189:19	65:23 66:6,13	194:4 195:17	287:16 292:1,3
102:1,1 129:18	206:22 309:13	66:17 67:1,14	196:10,17,20	293:23 294:6
129:19 134:21	309:14 341:12	67:19 68:2	197:10,14	294:18 295:18
134:21 216:8,9	<b>Kelly</b> 1:14 4:6	70:23 73:9,13	198:14,22	296:5,6,19
250:4,4 251:3	5:1 8:11,17	80:8,11,17,20	199:3 200:23	297:6,24
251:3,4,4	432:4 435:4,12	81:13 83:12	201:12,12	298:11,22
275:7,7 292:15	<b>Kenneth</b> 81:6	85:5,23 95:9	204:22,22	300:6,15,22
292:15 342:2,2	<b>key</b> 24:22,24	95:23 96:3,12	205:13 209:8	301:12 302:13
365:15,15,24	300:8	96:24 97:6	213:5 214:13	302:16,18
365:24 366:20	<b>khightower@l...</b>	98:3,4,4 100:3	214:15,16	304:23 311:3
366:21 367:2	2:4	100:15,16	216:1 218:21	314:17,21
368:20,21	<b>kick</b> 192:11	101:7,23 112:1	218:21 220:20	315:15,23
370:5,5 371:7	<b>kidneys</b> 314:19	117:12,13,23	220:21,23,24	317:6 318:11
371:7 372:11	<b>kind</b> 37:19	118:1,4 119:18	220:24 221:16	321:17 324:6,8
372:11 376:19	53:11 66:2	121:12,13,15	222:8,11,12,13	324:9,13
377:11,11	75:1 98:16	125:7 126:1,18	222:15,16,23	325:14 327:10
379:13,13	120:23 134:15	126:19,20	223:2 224:9,12	327:19 328:23
382:9 427:16	156:7 169:14	127:12,24	225:18,18,19	329:9,11,16,17



332:6 334:19	<b>known</b> 73:2,8	393:10 394:9	146:17,23	355:19 369:23
336:2 337:9	198:5 226:17	400:19	148:1 149:1	373:1,4 375:11
339:2 340:11	355:14,15	<b>larger</b> 420:20	152:13 157:16	395:4,11
340:23 342:3	<b>knows</b> 341:10	422:14	167:20 180:22	425:24 426:4
342:21 343:7,8	<b>Krekeler</b> 285:9	<b>larynx</b> 369:14	180:23 183:9	426:12
345:11 346:1,2	285:20 286:1,6	370:7	202:21 204:1	<b>LHG</b> 1:5
348:9 353:2,19	286:10 287:13	<b>Lash</b> 85:11	206:6 217:21	<b>LIABILITY</b> 1:5
353:22 354:1	287:20	<b>Latin</b> 80:8,9,10	224:15 226:9	<b>library</b> 103:24
360:16 364:20	<b>KRISTIE</b> 2:3	<b>lattice</b> 424:2	240:3 252:4,21	104:1
365:5,11 366:7	<hr/> <b>L</b> <hr/>	425:7,12	261:9 262:21	<b>lifetime</b> 416:4,9
367:3,10,23	<b>lab</b> 289:10	<b>launched</b> 204:7	279:23 285:15	<b>lightheartedly</b>
368:4,11,21	<b>label</b> 50:24	<b>law</b> 128:18	300:19 309:14	223:22
371:9,15,17,19	354:16 355:9	<b>lawsuits</b> 417:6	311:23 324:23	<b>limited</b> 116:22
373:3 374:1,21	355:10 360:4,5	<b>LAWYER'S</b>	326:7 331:22	184:8 188:13
375:17 377:2	362:9	4:12 436:1	352:6 362:10	312:9
378:6,19	<b>labeled</b> 82:14	<b>Lawyers</b> 28:8	369:4,6 386:18	<b>limits</b> 133:11
379:14 381:11	108:22 109:12	146:21	394:23 401:4	355:2 425:16
382:24 384:12	<b>labeling</b> 7:4 56:5	<b>lay</b> 75:21 76:14	405:13 420:17	<b>line</b> 222:9
386:2,23	351:14 353:5	331:23	422:11	247:17 258:10
387:16 391:14	354:2,20 355:7	<b>layman</b> 344:13	<b>letter</b> 6:13,15,17	288:23 428:23
392:16,22	356:20 357:10	<b>layman's</b> 323:3	6:19,21 224:18	434:2 436:3
393:14,24	358:6	<b>lead</b> 159:23	225:3 231:8	<b>lines</b> 49:1
394:18 396:11	<b>labels</b> 54:17	172:12 174:20	232:20 234:9	257:21
397:15,17	57:1 355:3	286:21	234:13,18,19	<b>linking</b> 257:1
398:2 399:2,5	<b>laboratory</b>	<b>leading</b> 80:22	234:19,21	<b>list</b> 52:24 69:9
399:13 400:17	408:14 409:1	<b>leads</b> 218:12	235:7,13,15	69:13,17 70:3
401:6,9,9,10	<b>lack</b> 365:24	<b>leak</b> 131:17	236:4,6 237:10	71:11,17,18,19
401:14 402:8	<b>Lake</b> 2:5 9:1	<b>leaking</b> 131:19	237:20,21	72:2,4 87:13
402:12,24	<b>Lane</b> 3:21 8:4	<b>led</b> 9:4 285:18	238:4 239:9,11	117:7 143:2
404:12 405:7	<b>language</b> 25:21	<b>left</b> 75:5,10	261:13,20	164:8 193:2
408:1,8,20	70:14 74:16	100:1 163:17	262:22,24	194:12,24
410:14 411:18	77:17 148:8	277:3 291:9	263:14 279:22	205:5,8 255:15
417:1 418:12	158:17 161:1,9	400:8	280:3 281:20	395:7 415:20
419:3,19	172:16 181:15	<b>LEIGH</b> 2:8	281:24 293:7	418:8
421:11,19,24	199:18 297:9	<b>leigh.odell@b...</b>	293:11 294:1	<b>listed</b> 12:11,22
422:7 424:15	326:10,21	2:9	294:15,17	13:19 14:2
425:11,14	400:6 408:22	<b>length</b> 431:6	297:8,9 302:17	68:13 83:6,16
429:4,24 430:4	<b>large</b> 16:22	<b>lenient</b> 358:1	327:11 328:13	87:19 101:16
430:5,7 431:9	42:21 130:1	<b>lens</b> 211:11	329:7 340:15	104:11 106:24
<b>knowing</b> 51:11	143:15 205:12	<b>let's</b> 12:17 22:6	<b>letters</b> 283:13	117:4 151:2
222:2 264:6	252:13 253:3	29:6 61:7 69:7	<b>level</b> 56:15	196:6 216:14
<b>knowledge</b>	253:21 260:4	71:23 75:3	126:14 295:3	265:21 356:18
34:12,17 42:11	286:16 310:18	82:11 85:18	344:2 370:18	356:19 358:5
95:5,8,10,14	311:17 312:14	86:6,6,19,22	370:21 371:3	362:8 390:23
103:8 172:16	313:11,24	87:20 107:10	426:20 427:5,6	393:3 423:5
224:10 314:4	321:6 353:1	107:22 135:8	<b>levels</b> 126:21	<b>listening</b> 201:14
316:12		144:18 146:11	152:16 314:10	<b>listing</b> 7:7

191:19 386:12	259:2,5 261:2	<b>loan</b> 162:1	143:3 144:23	292:10 299:24
<b>literally</b> 64:17	265:18 266:4	<b>loans</b> 63:12	145:2 146:11	300:10,11,15
<b>literature</b> 11:18	267:2,15 268:1	<b>localized</b> 161:16	146:23 150:17	300:17,17,18
16:7,8 17:7	268:6 270:14	<b>locate</b> 197:23	151:9,14,15	300:23 301:7,7
27:11 28:7,22	271:9,10	<b>located</b> 92:8	153:2,9 160:4	301:11,15,18
30:23 37:19	275:21 337:20	<b>locomotion</b>	160:20 165:21	302:10,19,21
38:24 39:19	339:22 343:11	253:7 259:14	169:6 170:2,20	302:22 303:1
40:5 41:22	345:1,13 365:9	<b>lodged</b> 378:3	172:22 175:4	305:11 306:20
42:13 43:17	366:19 377:10	<b>long</b> 39:14,16,20	176:9,20 177:4	324:23 332:18
44:8,12,14	377:19 381:2	48:14 66:6	177:16 178:2	334:23,24
45:7,11,12,15	390:16 391:17	204:8 246:9	178:14 179:14	337:19 344:23
45:16,20 46:10	394:13 403:6	258:8 295:9	179:16 180:16	345:12 347:6
46:16 56:8,21	411:13 417:24	324:24 325:15	183:4 184:5,10	348:13,24
62:18 63:2,3,7	419:3	350:24 388:20	184:13 188:18	350:6 362:10
63:8,9,19	<b>litigation</b> 1:5,23	394:1 431:2	188:24 189:13	362:19 364:3
64:13,18,22	3:21 8:5,10	<b>longer</b> 194:4	189:18,18	365:8 366:18
65:18 66:1,4	9:15 12:20,23	<b>Longo</b> 366:23	190:15,21	366:22,24
67:20 68:1	13:17 14:3,5	373:20	191:1,6,6	367:10,11
70:20 71:9	15:2 32:15,17	<b>loogie</b> 323:3	195:10,15,17	368:24 370:14
73:4 90:6 91:1	33:23 104:4	<b>look</b> 11:18 13:23	196:8 197:18	376:6,8,22
92:14 105:5,18	127:13 132:22	22:6 27:18	197:24 199:6	377:14 381:1
106:11,16	137:19 138:9	36:23 37:8	200:2,12,22	382:6 386:4
108:7 112:2	139:2 211:10	39:7 40:21	201:2 203:12	389:16 390:12
113:14,16	211:17 215:16	43:19 45:21	204:20 206:6	392:12 395:6
115:23 116:14	229:24 264:10	48:8 50:18	208:7 209:7,19	403:16 404:1
116:21 117:20	292:2 302:2	52:10 53:16	211:21 212:17	406:6 411:24
118:2,8,11,15	376:22 379:7	56:21 58:22,23	213:10 214:1	412:12,16
118:23 120:18	<b>litigation-based</b>	59:10 60:3	215:19 217:21	413:21,22
120:19,24	416:19	61:2 62:3	224:15 226:7,9	415:19,23
121:7 125:3	<b>litigations</b> 13:19	63:22 64:2	227:3 229:12	424:18 425:3
126:6 130:20	<b>little</b> 18:9 30:18	66:21 67:10	230:6 231:7	<b>looked</b> 35:9
131:14,23	31:14 48:20	68:17 69:10	235:4,19,21	36:23 37:19
132:16 136:22	56:4 95:20	71:23 73:14	237:7 238:10	40:4 42:10
137:6 138:1,11	132:8 135:15	74:22 75:3	238:11 241:2	44:20,23 45:14
144:20 145:15	155:5 161:22	79:6 82:17	242:2,22 243:2	45:15 46:1
145:17 160:7	183:4 201:11	83:11 86:22	244:14,17	67:10,11,12
167:24 186:10	238:17 243:3	87:14 92:13,14	247:8,9,11	86:21 105:8
191:20 194:19	318:6,24	92:15 93:15	248:18,18	113:16 115:22
195:9,11	321:16 325:20	94:8,9 101:6	250:18 251:12	115:22 117:15
209:16 213:1	339:17 356:10	102:5,5 103:16	251:13 252:4	131:22 139:1
215:4 221:18	417:22	115:8 117:23	252:21 257:9	148:2 150:22
234:20 237:14	<b>living</b> 18:20 19:3	118:7,11,17	257:13 261:9	177:8 178:9,10
237:14 241:3	19:9,20 23:15	120:16,23	262:21 268:4	180:13 183:2
242:11 243:3	24:3 343:24	121:10,18,19	270:5 272:2	185:10 188:7
244:24 245:5	<b>LLC</b> 3:10,10	122:18 123:23	274:21 279:23	190:21 191:12
246:6 252:2	<b>LLP</b> 2:2,13,18	131:13 136:16	280:9 282:3	192:2,5 194:5
256:2 257:16	3:2,7,12	136:22 139:3	286:9 289:14	194:8,22

196:20 202:17 205:8 209:6 211:11 213:14 213:17 214:24 215:3,8 216:5 226:14 232:24 233:9 239:17 265:18 266:4 277:6 293:2,14 304:16 310:10 326:10 332:1,9 332:10 333:1 334:2 344:17 345:14 348:17 350:4 368:3 387:4,5 390:20 391:5,9 392:6 392:21 403:18 410:9 415:3 <b>looking</b> 39:2 46:10,15 53:13 55:17 56:11 64:8 67:16,16 75:4 83:21 90:7 92:5 96:4 98:3,9 101:13 110:2,4,5 112:2 117:3 118:15 121:22 122:16,24 128:2 137:24 139:21 144:12 145:2 149:21 150:12 151:6,7 151:10 153:21 154:5 155:7,15 155:18 156:18 158:14 160:23 164:17 169:10 169:11,13 173:16 178:7 181:12 183:6 184:8 187:19 188:22,23 189:21,22 193:17 195:6,8 195:10 209:9	209:22 210:2,6 224:13 227:15 230:5,18 236:15,16,17 237:10 238:8 238:18 244:7 244:24 245:3 245:11 246:18 248:21 256:2 256:13,15,21 257:10 258:10 260:15 266:24 276:16 281:16 283:6 292:7 295:3,7,20 300:10 307:22 325:13,21 329:22 333:13 345:22,24 346:2,6 350:11 369:11 372:19 374:9 375:7,8 379:5 380:15 389:12 393:1 393:11 394:10 394:15 395:18 404:9 405:7,16 412:19 414:20 415:17 416:12 416:16 429:9 <b>looks</b> 50:19 87:12 112:3 125:8 208:17 257:14 329:17 401:19 <b>loose</b> 284:18 <b>Los</b> 2:21 <b>lose</b> 49:24 <b>losing</b> 369:7 <b>lost</b> 50:1 356:10 373:13 <b>lot</b> 16:8 24:11 53:12 169:12 253:19 276:16 311:24 312:3,8 312:11 330:3 387:15 393:7	401:2 411:18 431:1 <b>lots</b> 36:2 <b>Louisiana</b> 2:5 9:1 <b>LUNDY</b> 2:2,2 <b>lung</b> 227:22 228:1 312:21 313:4,5 321:9 323:18 325:3,8 327:14 329:19 369:14 370:7 403:15 <b>lungs</b> 311:23 313:18 314:19 315:5 316:5 <hr/> <b>M</b> <b>M</b> 2:3 321:16 <b>M-A-L-M</b> 97:24 <b>ma'am</b> 120:22 <b>macrophage</b> 395:3,21 <b>macrophages</b> 313:9,16,18 314:3 316:3,19 317:3 321:20 322:9 <b>macrophages'</b> 316:5 <b>magnetic</b> 289:22 <b>main</b> 1:16 3:8 408:11,23 <b>maintain</b> 9:3 303:4 353:12 425:15 <b>maintained</b> 68:3 <b>maintains</b> 65:24 66:13 <b>majority</b> 383:24 426:17 <b>makeup</b> 216:17 <b>making</b> 41:20 44:5 98:10,13 98:13 378:16 <b>Malm</b> 97:24 99:1,14,21	101:3,19 <b>mammalian</b> 396:3,5 397:9 406:1 407:7,13 <b>man-made</b> 17:14 19:9,19 24:2 <b>manager</b> 281:20 341:19 342:1 <b>manner</b> 246:4 348:15 <b>manual</b> 17:24 18:6 19:14 20:14 24:9 405:14,20 410:8 <b>manufactured</b> 14:24 15:5,11 27:3,9 35:17 36:6 56:11 <b>manufacturer</b> 16:1 32:3 51:20 <b>manufacturers</b> 30:22 <b>manufactures</b> 36:2 <b>manufacturing</b> 49:8 291:12 <b>March</b> 178:19 262:24 263:1,3 <b>mark</b> 20:6 26:7 50:8 72:8 81:23 93:6 141:6 157:17 159:16 164:5 165:7 172:6 174:13 224:16 249:8 284:12 284:14 340:13 398:15 <b>marked</b> 9:8,11 10:15 12:5,8 17:19,23 20:3 26:10 50:4 72:12 82:3 93:10,13 94:1	102:17,22 141:10 157:21 159:20 164:13 166:12,16 168:5 170:10 170:14 172:9 172:20 174:17 183:11 190:9 197:3,7 201:18 201:21 217:10 217:16 224:19 235:8 249:12 250:19 252:8 261:14,20 273:9,13 279:24 280:4 280:22 284:21 293:5,8 320:18 320:21 340:16 347:23 348:2 351:15 352:20 362:11,14 386:8,13 398:19 399:22 415:7,10 416:2 419:9,12 <b>marketing</b> 1:4 66:7 <b>marks</b> 142:15 431:19 <b>married</b> 37:24 38:12 <b>master's</b> 97:19 <b>material</b> 21:23 54:15 91:21 92:6,7 316:20 355:8 360:3 362:6,9 371:12 <b>materials</b> 5:16 18:2 68:13,14 71:20 100:3 102:21 103:5,8 103:16,18 104:20 106:21 106:24 130:7 138:24 140:19 158:7 160:5
--	---	--	--	---

164:8 167:23	139:18 152:22	227:7,18	<b>medicine</b> 75:6	178:12 268:4
170:18 172:19	154:24 156:19	242:22 261:3	223:21 408:17	<b>methodologies</b>
174:5,24	157:8 166:19	305:8,12,14	409:4	27:22 28:5,20
183:12,24	177:11 190:21	315:8 318:13	<b>meets</b> 364:23	29:3 30:1
191:14 192:12	194:16 204:7	326:1,3 327:8	<b>member</b> 26:2	58:23,24 59:12
193:9 202:3,8	205:6 207:9	328:7,22 329:1	<b>membership</b>	59:23 60:4,6
202:19 203:4	216:21 220:13	330:18 331:14	26:18	60:12,15
205:22 216:12	235:4 240:24	333:9 334:9	<b>memory</b> 253:23	133:22 187:11
216:15 251:10	242:1,24,24	335:3 336:20	313:14 401:5	265:20 266:5
251:20 252:10	249:21 250:3	337:5,14	405:10	267:1,14
287:15 288:18	250:11 259:24	389:14 390:7	<b>mention</b> 117:12	270:12 288:22
290:13,18,22	276:15 279:2	395:16	123:15 153:19	303:21 380:20
312:7 360:2	283:9 295:9,22	<b>mechanism(s)</b>	190:2 207:10	<b>methodology</b>
365:10 374:20	297:11 303:24	207:1	338:22	27:1,2,13 28:1
384:16 389:17	305:17 309:2	<b>mechanisms</b>	<b>mentioned</b> 31:1	28:10,15 29:17
389:18 390:1	318:20 319:23	137:16 140:19	105:1 153:16	58:7,18 59:6
<b>mathematical</b>	319:24 322:20	140:22 141:3	173:16 199:22	59:19 60:14,18
406:23	344:3 358:18	227:24 305:23	247:23 253:20	60:22 61:2
<b>matter</b> 8:9 14:1	373:15 381:7	306:8 307:6,15	289:11 389:8	73:5 110:4
14:15 29:6	391:7 399:11	307:22 309:17	<b>mentions</b> 413:3	115:12,14
39:17 40:23	399:14,16	310:5 314:15	<b>mere</b> 92:3,5	117:22 119:11
158:8 160:8	401:7 402:5	314:17,24	242:23 243:6	123:1 185:19
168:1 267:7	404:6,7 421:16	315:4,10,17,19	<b>merely</b> 73:6	185:20 187:14
379:8 380:4,12	423:9 425:11	315:21 317:4	152:5 169:7	236:3 239:14
381:8,21,22	427:24 430:5	319:15,19	185:19 187:11	242:6 254:19
423:19	<b>meaning</b> 171:21	321:4 322:13	211:11 259:4	267:8 268:2,5
<b>matters</b> 13:9	191:3	322:22 323:13	303:20 345:14	268:13 269:2
41:9 52:22	<b>means</b> 45:21	329:22 330:1,6	401:16	270:20 272:3
381:7	80:11 106:16	330:10 332:1,5	<b>mesothelioma</b>	298:4 346:20
<b>maximize</b> 171:2	108:14 109:5	332:7 334:16	369:13 370:7	347:3,6,9,14
<b>mays</b> 220:20	151:19 156:2	337:21 338:16	<b>Messel</b> 13:6	347:19 348:15
<b>McDonald</b> 6:7	166:20 191:3	340:5,7 346:4	<b>messengers</b>	348:16,20,23
174:16,21	198:22 262:20	396:12	323:23	348:24 349:3,9
178:16,24	299:11,13,18	<b>mechanistic</b>	<b>met</b> 8:23 33:4	349:16,21,24
179:20	315:24 328:23	181:8 306:3,18	<b>meta-analysis</b>	367:9,11 368:8
<b>MDL</b> 1:4 8:10	381:10 401:9	330:10 334:2	202:24 208:15	368:13,24
104:4	401:10	<b>mechanistics</b>	208:21	371:18 426:7
<b>mean</b> 11:2 35:2	<b>meant</b> 36:4	337:17	<b>metal</b> 285:13	<b>methods</b> 196:11
37:6 42:13	70:13 92:20	<b>media</b> 41:11	424:11	210:3 269:6
46:9 56:14,15	157:14 207:11	42:3 43:8,17	<b>metals</b> 287:22	271:5,8,8
57:19 71:13	222:24 249:18	43:21,24 44:6	289:20,23	288:6,8,9,12
73:1 79:20	338:12 339:1	44:16,19 45:2	292:11 423:22	288:15 289:9
80:7 88:13	401:11 404:19	45:5 46:19	423:23,24	<b>metrics</b> 343:24
90:22 91:22,24	<b>meat</b> 154:7	403:5,5 417:4	424:5,8,15,19	<b>Michael</b> 1:18
92:6 97:16	<b>mechanism</b>	<b>mediators</b> 324:3	424:23 425:8	2:19 3:7 99:8
101:2 121:20	113:5 212:22	<b>Medical</b> 384:20	<b>method</b> 163:4,9	<b>michael.ander...</b>
131:15 134:4	226:16,16	385:2	169:9,12	3:8

<b>michael.zeller...</b> 2:19 <b>MICHELLE</b> 2:13 <b>mid-sentence</b> 124:19 206:21 <b>middle</b> 83:4 301:19 322:1 326:12 <b>migrate</b> 88:16 89:3,10,24 91:6 107:14 110:11,15,19 110:24 111:4,8 111:23 112:15 113:20 114:9 116:8 119:9 120:11 124:16 126:7 135:19 137:1 139:14 139:23 173:5 175:8 195:8 206:9 211:13 213:15 214:4,9 228:5,24 230:11 232:4 233:21,21 242:18 244:19 253:8 303:17 322:14 333:4 334:1 <b>migrates</b> 111:13 305:5 <b>migrating</b> 111:19 <b>migration</b> 88:3 89:6 90:14,20 91:4,20 107:11 107:13 108:2,5 108:14,23 109:5,13,14 110:3 111:17 112:6,19,24 113:9,24 116:6 116:13,22 117:1,5,8,14 117:17 119:8	120:6 123:7,18 124:15 125:5 125:12 127:7 127:11,18 128:4,6,23 129:14,21 130:15,20 131:23 132:1 132:17,23 133:9,13,16 134:6,23 135:11,18 136:11,17 137:9 142:7 145:22 149:17 150:8 164:19 164:19 169:11 169:20 171:13 173:1 176:2 177:10 179:2 179:23 180:20 184:18,19 185:24 186:5 186:15,20 192:7,9 193:7 193:7 194:10 195:6,13,24 196:5 204:16 208:20,23 209:10,14,22 210:6,20 211:12 212:23 213:2,9 216:7 218:7 220:16 221:23,23 229:16,20 230:10 232:3 232:13 233:10 239:4 241:16 242:16 243:10 243:10,19,23 243:23 245:8 260:18 293:18 303:7 304:2,9 304:17 305:3 332:9,12,16 333:1,15	337:15,16 <b>Mike</b> 8:15 <b>Miller</b> 1:18 8:15 32:21 432:2,18 <b>millions</b> 64:9 113:13 191:24 <b>Mills</b> 293:20 <b>mind</b> 40:8 70:4 74:19 93:20 122:12 124:7 145:9 160:11 228:2 301:24 <b>mine</b> 38:17 39:19 290:24 <b>mined</b> 290:19 292:3 <b>mineralogist</b> 292:24 293:1 366:3 368:12 <b>mineralogy</b> 366:5 <b>minerals</b> 162:21 289:23 <b>mines</b> 292:14 <b>minute</b> 179:15 275:12 <b>minutes</b> 85:18 158:23 182:19 280:16,18 351:3 <b>misguided</b> 84:10 <b>misinform</b> 421:2 422:6,21 <b>misquote</b> 156:10 403:4 <b>missing</b> 116:20 <b>misspeak</b> 344:14 402:20 403:3 <b>misstates</b> 194:14 276:6 303:11 303:11 329:14 357:18,18 <b>misunderstood</b> 193:1 <b>mitigate</b> 22:10 46:2	<b>mode</b> 418:3 <b>model</b> 397:21 398:9 <b>models</b> 383:3 387:9 390:24 398:4,4 <b>Modern</b> 5:12 80:15 81:11,15 81:22 82:2,13 82:16 84:2 <b>molecular</b> 130:4 132:12 207:1 341:20 <b>moment</b> 12:1 50:2 65:9 87:15 92:19 124:20 135:9 160:14 169:2 180:23 198:3 209:14 326:7 346:10 386:19 392:12 410:9 413:10 <b>moments</b> 8:24 37:14 <b>monograph</b> 5:18 7:6 141:10,21 142:22 143:9 143:10,11,18 144:13,22 145:5,10,13,15 145:20 146:2,6 148:2 180:24 181:3,3,6 182:5,11 184:24 187:16 188:10 189:3 190:6 362:13 363:4 369:5,17 <b>monographs</b> 363:16 <b>Montgomery</b> 2:10 <b>month</b> 33:5,7 <b>months</b> 403:9 412:21	<b>Moore</b> 33:19 <b>Moore's</b> 33:20 372:2 <b>morning</b> 8:21,22 218:3 <b>mother</b> 36:10 <b>mouth</b> 169:22 <b>move</b> 136:21 137:22 163:2 169:19 196:15 247:5 279:24 358:8 <b>movement</b> 148:22 149:10 149:16 150:5 150:13 151:13 151:19,24 152:12 156:23 <b>moving</b> 161:22 246:8 428:18 <b>mparf@aol.co...</b> 2:14 <b>MSDS</b> 355:9 356:18 357:8 <b>Mucociliary</b> 322:18 <b>mucous</b> 323:24 <b>multiple</b> 60:6 126:5 331:5 <b>music</b> 201:14 <hr/> <b>N</b> <hr/> <b>N</b> 2:1 3:1,2 <b>N.W</b> 3:13 <b>Nadia</b> 33:18 <b>name</b> 8:4 33:21 33:22 34:14 35:12 63:17 81:3,6 97:13 99:9 219:1 249:3 250:21 283:18 293:13 302:1 327:24 341:14,21 <b>names</b> 47:4 96:13,23 101:12
--	---	--	---	---



<b>narrow</b> 35:23 126:12	84:21 85:5 86:2 108:21	<b>never</b> 70:12 205:8 228:2	358:9 431:2 <b>nonresponsive...</b>	400:9,17 401:12,24
<b>Nation</b> 63:17 97:1,2	114:15 117:10 123:10 139:19	420:18 422:12 <b>new</b> 1:1 3:4	431:6 <b>Nony</b> 6:20	404:3,12,14,17 405:6 412:18
<b>National</b> 197:17 198:5,8,10	143:3 144:7,23 146:16,17	22:18 23:8 25:14 201:9	320:17 <b>normal</b> 106:15	414:11 <b>NTPC</b> 404:16
199:7 200:8 222:16 404:24	151:14 157:12 160:20 173:18	223:21 253:18 259:3 304:23	142:10,18 144:3,4,10	404:18 <b>nu-</b> 136:14
<b>Nations</b> 350:19 352:10,21	178:13,21 190:23,24	<b>newborn</b> 36:10 36:15 42:7,13	147:3 149:24 185:5 252:14	<b>nuances</b> 42:2 128:23 129:15
353:14 354:17 359:6	191:6,18 193:15 195:17	380:6 427:16 429:14	253:4 260:5 344:18,21	405:10 <b>Nucor</b> 55:12
<b>natural</b> 17:14 19:19 24:2	196:7 204:19 208:16 231:6	<b>news</b> 34:19 35:14 37:17	345:4 389:10 <b>normally</b> 182:10	<b>number</b> 5:3 14:8 15:18 16:22
49:24 <b>naturally</b> 15:18	237:7 238:3 241:21 242:2	42:16 384:11 <b>Newton</b> 5:19	<b>Notary</b> 1:20 432:3,21	68:21 87:8,11 87:12,18,19
19:9 <b>nature</b> 63:13	242:22 246:15 246:21 248:4,8	128:19 157:20 182:5,9,16	435:20 <b>note</b> 10:14 116:3	92:24 94:9 130:1,5 161:6
67:3 100:19 213:12 214:20	248:14,17 251:11 252:16	183:21,22 184:5,10 188:1	159:3 162:14 163:6 205:20	176:11,13 190:12 205:12
214:20 277:11 419:17,18,19	258:8,9,10 260:6,12,13	188:15 189:20 <b>nine</b> 72:2,5,5	218:1 219:7 222:10 409:9	223:13 253:22 254:8 275:8
420:12 <b>NCI</b> 197:14,15	268:22 276:24 280:7 286:9	73:19,23 74:8 75:13 76:3,20	414:22 416:3 416:13 430:24	286:16 288:22 311:17 313:2
197:16 198:21 199:18	298:22 300:15 300:16 304:20	77:5 78:13 79:6,7 80:1,1,4	431:13 <b>noted</b> 8:12 18:1	313:11 314:1 314:14 317:10
<b>NCRA</b> 432:19 432:19	324:19,20 335:16 338:3	83:3,15,18 87:10 114:22	26:18 169:23 288:6 327:4	336:6 346:14 346:17 351:10
<b>near</b> 204:2 322:13 362:17	342:19,20 344:15 347:7	115:5,8 203:22 227:3,15	387:8 388:13 392:4 416:7	399:2 404:5,8 416:4,8
<b>nearing</b> 86:1 <b>necessarily</b> 40:3	350:6 356:17 356:19 362:16	233:11 300:3 <b>ninth</b> 20:12,15	417:1 433:11 435:7	<b>numbered</b> 217:11 306:22
44:18 50:11 91:20 139:18	377:23 389:11 395:16 396:8	23:2,4 <b>non</b> 74:12 77:19	<b>notes</b> 4:12 39:10 39:11 436:1	<b>numbers</b> 75:8 94:7 101:9,11
240:24 241:24 303:2 316:22	396:17,23 397:16 403:16	80:7 <b>nonasbestos-c...</b>	<b>notice</b> 165:13 176:7 390:10	252:13 253:3 260:4 310:18
392:20 428:2 <b>necessary</b> 10:3	406:17 408:3 413:21,22	350:15 352:2 352:10 353:15	<b>noting</b> 73:20 244:13	312:14 321:7 411:11
51:2 56:18 84:12 170:24	415:5,6 <b>needed</b> 410:4	353:18 354:9 356:14 357:3	<b>November</b> 32:20 33:2	<b>numerous</b> 157:11
288:1 290:3 431:5 433:4	<b>needs</b> 85:23 410:5,15	357:16 359:5 359:13 360:15	40:1 282:8 <b>NRC</b> 59:19	<b>nurse</b> 146:16
<b>need</b> 21:22 50:18 53:15	<b>negative</b> 79:17 <b>neither</b> 109:8	<b>nonexistence</b> 330:17 331:13	60:13,22 <b>NTP</b> 7:8 218:14	<b>O</b>
56:15 60:3,7 60:17 73:14	180:12 420:22 422:16 432:13	<b>nonlitigation</b> 384:1	222:8,12,16,20 222:24 398:17	<b>O</b> 172:15 <b>O'DELL</b> 2:8
74:24 83:10,20	432:14 <b>nonresponsive</b>	<b>nonresponsive</b>	398:21 399:8	<b>o0o--</b> 431:24 <b>oath</b> 9:17

<b>obeyed</b> 75:23 76:16	172:1 173:8 174:7 175:18	290:8 291:7,21 296:3,17	384:9 387:14 388:1 389:1,6	375:11,22 376:7 378:20
<b>object</b> 273:19 398:8	177:23 179:5,9 180:7 182:23	297:15,18 298:18 299:7	390:14 391:10 392:15 393:18	379:1 <b>occupationally</b>
<b>objection</b> 15:13 16:4,20 19:15	185:17 186:7 187:1 188:20	299:22 301:10 303:10 306:1	395:13,23 396:21 397:23	13:21 <b>occur</b> 139:19
21:6 24:20 25:12 28:18	189:9 190:16 191:16 192:18	306:11 307:17 308:2,11,20	398:10 406:10 407:10,23	210:12 241:1 242:2 243:1
29:8,21 30:6 31:12,21 40:18	193:11,24 194:13 195:1	310:21 311:9 313:23 315:14	410:11,22 412:7 413:2,13	311:6 317:9 408:6
41:18 42:8 43:2,13 44:17	196:22 199:9 199:21 200:10	316:7 317:8 318:1,5 319:9	414:14,18 416:20 418:23	<b>occurring</b> 15:18 19:9
45:17 46:14 47:9,18 48:11	204:18 205:9 208:3 209:3,18	323:9 324:16 325:6 327:9	421:8 422:24 425:9,19	<b>occurs</b> 260:18 362:3 408:5
49:5 51:6,23 52:8 53:5,23	210:18 211:2 211:23 212:9	328:11 329:4 329:13 330:22	426:22 427:8 427:18 428:6	<b>October</b> 33:7 39:24 294:1
54:22 57:8 58:21 60:1,24	214:11 215:1,7 219:10 220:11	331:2,16 332:3 332:21 333:11	428:24 429:6 429:19 430:3	<b>odd</b> 223:23 <b>odds</b> 294:19,22
61:19 62:2,14 64:4 65:1,22	220:17 221:13 221:24 222:22	334:5,13 335:7 335:12,15,23	430:11,19 <b>objections</b> 378:2	294:24 295:6 295:18,23
66:9,19 67:23 68:10 74:5	224:6 225:16 226:5,18 229:3	336:4,22,23 337:8 338:2	380:8 <b>objective</b> 210:6	296:7,16,18,19 297:7,17,21
77:20,24 78:18 79:2,14 80:24	230:2,17 232:18 233:6	339:8,16 340:1 342:18 343:6	236:18 <b>objectives</b>	298:1,8,24 299:4,20 300:6
84:16 88:22 89:15 90:16	234:11,23 236:7 238:6	344:6 345:6,10 345:21 347:16	165:22 177:5 196:11 211:19	300:14,16,18 300:22 301:12
91:18 92:2,11 103:10 104:22	239:16 240:21 242:3,7 243:12	348:18 349:6 349:22 350:5	<b>obligation</b> 51:20 52:3	301:13 <b>offer</b> 11:13
107:5 108:17 109:1 112:9	245:17 246:14 247:6 248:3,13	354:11 356:6 356:15 357:5	<b>observational</b> 404:20	14:23 84:20 129:20 154:20
113:1 114:14 117:9 118:13	250:13 251:5 254:4 255:17	357:17 358:13 359:14 360:8	<b>observations</b> 163:14	156:3,6 165:24 166:8 175:1
119:15 120:7 121:24 122:8	256:10 258:3 258:13,19	360:17,24 361:21 365:4	<b>observe</b> 223:20 <b>obstacle</b> 71:8	212:8 278:1 299:20 330:16
122:21 123:9 126:16,22	259:8,21 260:9 263:11,22	365:17 367:7 367:21 368:17	<b>obtain</b> 285:22 342:12	331:12 336:18 357:22 359:8
127:21 128:13 129:22 130:18	264:16 265:3 265:16 266:7	370:9,23 371:5 371:8 372:4,12	<b>obviously</b> 73:2 163:16 164:2	360:7 366:4 382:21 418:14
132:3 133:14 134:7,11,16,24	266:11,18 267:11 268:10	373:9,24 375:6 375:15,19	302:24 350:3 385:6 431:8	418:16 <b>offered</b> 77:16
138:16 139:9 140:6,15,24	269:4,14,23 270:22 271:20	376:2,16 377:4 377:8 378:10	<b>occasions</b> 157:12	212:11 230:15 427:20
145:23 153:15 155:1 156:16	271:23 272:15 274:16 275:19	378:18 379:10 379:23 380:9	<b>occupational</b> 75:6 354:18	<b>offering</b> 100:13 166:7
166:10 167:12 168:20 169:21	276:5,21 277:4 278:2,21 283:4	380:14 381:9 381:23 382:4	355:19,23 369:23 370:12	<b>offers</b> 46:1 218:6 379:15
169:22 171:16	286:7 288:4	382:23 383:12	373:1,4 374:2	379:17

<b>offhand</b> 355:21	153:11 154:3	424:21 425:15	303:12 331:13	248:9 286:1
<b>office</b> 18:7,8,10	159:7,11,15	427:14 430:23	333:7 334:8	<b>ore</b> 289:19
18:11 420:1	160:21 161:21	431:8	336:18 337:3	290:13
<b>official</b> 218:4	162:10 164:17	<b>old</b> 281:1	373:15 379:15	<b>organ</b> 91:21
<b>oh</b> 35:19 123:14	164:24 165:6	<b>older</b> 363:21	423:4,8,14,24	92:8 139:17
161:24 164:24	165:17 167:8	<b>omit</b> 77:17	<b>opinions</b> 67:2	210:11 314:20
177:17 198:17	167:20 168:18	163:21	100:12 113:3	314:21
401:1 404:21	169:18 171:14	<b>once</b> 125:15	122:18 129:21	<b>organisms</b> 17:11
421:14 422:2	171:20 174:1	309:12 341:8	133:6 134:10	18:20 19:3,10
<b>Ohio</b> 3:9	176:24 180:22	<b>one-page</b> 20:7	135:5 146:9	19:20 23:16
<b>oil</b> 13:3 14:7,10	181:21 184:22	102:24	166:7 175:1	24:3 343:20
<b>okay</b> 10:4,19	186:21 197:2	<b>one-paragraph</b>	199:20 212:10	344:1
14:1,22 33:18	198:21 199:2	306:22	212:15 218:21	<b>organization</b>
35:16 36:20	201:9 202:16	<b>ones</b> 44:9 103:18	222:3,4 230:14	222:13 364:23
38:2 39:10	202:21 203:12	103:21 104:8	254:14 255:6	<b>organizations</b>
44:7 45:4,10	204:14 205:17	188:10,11	256:20 263:20	223:1
46:21 47:6	206:6 216:15	189:15,15	264:10 269:10	<b>organizing</b>
49:18 51:15	217:21 225:12	363:21 394:18	269:17,18	100:2
52:17 59:4,15	226:1,9 235:4	<b>ongoing</b> 131:7	270:16 278:3	<b>organs</b> 148:15
59:18 60:20	240:12 241:22	401:21,22	303:9,14,18	314:10,18
66:12 67:5	245:21 246:2,5	<b>Oops</b> 322:4	304:8 319:1	315:3 329:24
68:5 69:19	250:17,22	<b>open</b> 124:4	330:17 337:9	<b>organs'</b> 314:24
71:3,23 72:7	252:12 261:19	175:9 218:8	343:5,7 366:4	<b>original</b> 76:12
75:3 79:19	262:2,8,21	281:9 359:5	376:3 382:3	105:8 144:9
81:10 83:7,14	278:9 280:17	<b>opened</b> 95:6	427:19	202:19 433:15
84:1 85:9,17	280:19 281:18	<b>opening</b> 167:4,7	<b>opportunity</b>	<b>originally</b> 385:7
85:21 86:15,23	283:16,21	167:11	70:7 165:24	<b>ORs</b> 294:13
87:5 89:5	285:15 293:2	<b>opine</b> 236:8	170:2 171:6	<b>OSHA</b> 354:17
90:10 92:18	294:21 295:22	<b>opines</b> 109:4	176:6 177:16	364:24
93:2 94:21	298:21 305:14	<b>opinion</b> 11:13	193:13,18	<b>outlined</b> 65:9
97:8 100:7	305:21 309:8	14:24 42:23	336:16 348:13	158:21 279:17
102:15 103:23	312:14 313:8	78:21 108:3,12	390:11	<b>outside</b> 18:12
104:10 105:7	315:11 317:20	108:23 109:8	<b>opposed</b> 43:5	126:14 138:5
105:12,19	321:21 323:1,4	109:12 112:6	90:3 100:8	212:9,14
106:3 107:7,10	324:13 338:24	112:23 113:9	155:15 159:6	258:11 365:17
109:11 115:17	339:21 340:12	145:16 169:20	173:14 189:23	376:2 379:11
116:11,24	342:5 343:2	193:23 208:24	243:6 245:2	427:18
117:19 119:10	344:12 350:2,9	213:2 215:5	335:18 371:20	<b>ovarian</b> 6:8 9:5
120:14 122:12	352:18 356:8	264:18,24	377:17 428:8	11:15,22 27:20
123:4 127:3	362:21 363:13	265:5 266:6,10	<b>opposite</b> 278:13	29:13,20 30:12
129:1 133:2,20	364:14 369:4	266:17 267:6	<b>opposition</b>	42:22 45:9
137:5 141:5	372:15 379:24	267:13,22	117:5,8,14	57:14 62:22
143:6,19,21	383:2 388:18	268:9 269:3,22	125:5	65:21 66:24
144:1 146:11	395:10 397:12	270:20 271:16	<b>options</b> 15:19	68:9 88:1 91:3
146:17,19,20	399:21 401:23	271:17 277:22	274:11	91:14 149:6
147:10 149:1	402:21 415:19	277:23,24	<b>order</b> 40:15	153:18 161:12
150:3 152:2,13	416:1,18 422:2	295:10 298:14	141:16 151:12	162:17 197:6

199:12 206:10	426:9 430:18	327:12 332:13	87:5,15,21	410:9 412:20
206:16 207:2	<b>ovaries</b> 88:2,3	333:5,16 334:1	96:5 101:14,15	413:9 415:23
209:1,7 210:16	88:13,17,21	334:3 336:21	107:11,20	416:13 418:22
211:1,6 212:7	89:3,10,14	382:22 410:21	108:10 114:17	419:1 420:14
212:19 218:10	90:1,7,19 91:7	<b>ovary</b> 108:6	123:23 124:10	421:14,15
218:15 222:21	91:9,12,16	163:13 233:21	124:13 125:9	434:2 436:3
226:13 230:24	107:17 108:13	245:16,23	125:20 135:8	<b>pages</b> 71:23 72:1
232:9 233:15	109:5 110:12	315:20,21	136:15 142:2,3	83:19 96:7
236:11 242:13	110:15,21	332:2,5,7	143:20,23	102:5 180:11
244:1,2,9	111:5,10,19	369:14 370:8	147:5 148:1,3	202:21 358:19
245:4,13,16,22	112:7,16	376:1 378:17	148:6 158:3,17	358:19 359:11
246:11,19	113:21 114:9	<b>overall</b> 116:14	158:18 160:10	368:16 379:20
247:1,4,21	116:10 119:9	127:10 132:14	160:23 161:8	383:4 402:10
248:23 252:14	120:12 126:9	163:8	161:24 162:23	411:4,10,21
252:24 253:4	130:23 137:1	<b>overarchal</b>	163:7 164:18	435:5
257:2 260:5	138:2,23	237:11	164:23 168:6	<b>paid</b> 411:8
263:8 264:13	139:15 140:23	<b>overarching</b>	170:20 172:23	<b>paper</b> 72:23
264:21 265:24	142:10,17	225:24 236:9	175:5,14	73:11 74:16,22
268:19 272:13	144:3 147:3	<b>overhead</b> 409:7	178:18 181:10	76:12,22 83:8
274:10 275:24	148:24 149:11	<b>overly</b> 52:14	181:11,19,22	104:19 105:14
276:11 281:5	149:22 150:2	<b>oversaw</b> 367:14	182:3 185:1,11	105:24 106:4,7
293:21 306:4	152:1,6 173:15	<b>oversee</b> 99:1	185:13,22	114:23 115:17
306:19,24	175:10 176:4	<b>overseeing</b>	187:3 190:5	158:19 159:16
307:10 308:5	179:4,23	98:22	199:6 203:15	160:1,21 161:7
308:15 310:14	184:14,20	<b>oxidative</b> 388:22	204:1,3,10	161:20 162:6
328:4 330:13	185:4 186:1	389:4	206:7 207:16	162:15 163:1
330:18 331:15	190:2 192:8	<b>oxygen</b> 324:2,4	207:19 212:3	164:6 165:7
332:20,24	195:8,13 196:1	324:9,14	217:22 223:19	167:21 168:4
333:9 335:1	199:15 206:12		226:9 235:4	172:12 174:20
336:20 337:7	208:18 209:17	<b>P</b>	252:22 257:13	174:23 179:1
337:13 343:15	210:5,8,10,15	<b>p</b> 2:1,1,8 3:1,1	274:6 282:3	179:20 180:3
345:17 355:16	211:14 212:23	262:10 278:19	289:13,18	182:7,21 183:2
355:20,24	213:6,16,23	279:4 293:15	290:7 294:15	183:10,16
356:5 365:7	214:5,7,10	420:19 422:14	301:18 302:10	184:5 190:9,15
369:24 370:13	215:6,14 228:9	<b>p.m</b> 147:17,19	306:21 321:3	191:12 194:7
370:16 372:21	230:11 232:5	240:6,7,8,10	322:14 326:9	202:7 203:3,9
373:2,7,17,18	232:15 233:11	284:1,2,3,5	334:23 338:13	203:20 204:11
373:22 374:4	240:17,24	364:8,9,10,12	341:17 350:10	207:11 212:2
374:10 375:1,8	241:7,16,23	431:21,23	351:24 352:22	218:2 219:4,15
375:11,12,18	242:19,21	<b>page</b> 5:3 13:6	352:24 353:3	219:24 220:5
376:8,10 378:1	244:13,14,19	14:13 18:14,17	355:1 357:14	221:21 223:5
378:15,21,24	244:22 248:17	20:9 22:6	363:24 369:9	249:16 250:23
379:2 381:3,17	249:1 253:11	25:20 68:17,19	388:14 389:22	252:6,8,15,23
382:18 390:18	260:20 303:18	70:10 71:12,14	392:5 395:1	253:16,17
397:22 398:4,4	304:18 305:5	73:17 74:19	399:21,24	256:6 257:23
398:8 403:20	314:19 315:5	75:4,8,9 82:7	400:1 401:12	274:20 275:2
411:16 425:18	315:10 326:16	82:12 86:24	405:16,19	275:15 278:7

293:18,19,24	388:14 389:23	171:12 185:24	155:16 165:18	198:22 199:3
294:2 327:4	395:2 400:7	186:5,15,20	184:12 185:22	<b>PDR</b> 6:9 197:7
354:8	402:11 406:7	312:19 318:4	188:3 207:19	<b>peer</b> 98:6,8
<b>papers</b> 116:19	420:16 421:10	364:22	207:21 208:10	<b>peer-reviewed</b>
169:18 183:21	421:17,17,18	<b>particles</b> 88:2,12	211:3,15 227:2	68:1 105:5,18
192:23 193:4	423:3	88:20 89:2,9	229:14 237:9	237:14
220:2 251:9	<b>paragraphs</b>	89:11,13,23	238:13,22	<b>pelvis</b> 206:9
252:9	125:19 188:4	90:2,7,9,19	239:19 240:1	<b>people</b> 100:21
<b>paragraph</b>	383:6,7	91:6,9,12,16	254:24 255:1	130:8 271:16
18:16 22:7	<b>Paralegal</b> 3:18	107:13 112:1,3	292:14 300:22	<b>perform</b> 58:4
25:10,20 50:19	<b>parallel</b> 98:23	136:24 138:3	323:15 325:13	60:16 126:24
75:12,18 78:15	<b>parameters</b>	140:5 148:23	329:20 355:5	<b>performance</b>
82:18,22 83:3	92:16 395:17	149:10 150:6,8	359:19 370:14	58:9 289:5
83:5,17 84:2	<b>paren</b> 281:9,9	151:19,24	378:5 402:11	<b>performed</b> 58:5
109:2 124:12	359:6,7	156:23 158:21	403:14 404:10	59:15 118:5
135:10 146:12	<b>parenthetical</b>	159:5,12 161:1	414:19	254:20 255:10
148:8,11 149:2	161:15 352:14	161:3,15	<b>particularly</b>	<b>performing</b>
151:2,20 152:8	<b>PARFITT</b> 2:13	162:19 163:5	38:18 108:1	295:4 342:24
152:9,14	<b>Park</b> 3:4	169:7,8 178:10	205:18	<b>perineal</b> 11:21
154:13 168:7	<b>part</b> 24:18 27:13	182:17 183:5	<b>particulate</b>	15:20 30:11,20
175:6,14 180:9	31:8 47:15	184:11 189:21	228:8 326:15	32:1 62:21
181:13 182:3	51:8 53:6	206:8 210:24	<b>particulates</b>	65:20 66:23
187:3,9 188:3	56:13 77:4	212:6 228:4	228:24	68:7 88:15,18
188:15 190:5	81:18 87:1,23	247:3,21 249:1	<b>parties</b> 432:13	89:1,8 91:2,4
203:13 204:2	102:17 115:13	252:14 253:3,6	<b>parts</b> 331:5	107:15 108:15
206:19,23	117:21 118:3	259:13 260:5	354:23	109:7 110:10
207:7,23	119:11 122:2	260:12 281:5	<b>party</b> 432:11	110:14,18,23
208:10 223:18	123:5 126:1,4	310:18 311:5	<b>pass</b> 213:21	111:3,7,15
226:11,11	127:9,22 128:1	311:17 312:15	<b>passing</b> 175:8	112:7,14
228:4,16,21	128:15 129:5,7	313:20 316:4,6	420:10	113:19 114:7
230:4,14,23	131:7 132:10	317:1,15 319:7	<b>pathologies</b>	116:7 119:8
232:12,20	132:14 137:2	321:7 322:16	152:19	120:10 123:8
235:1,1,6	145:1 203:6	323:16 325:1,2	<b>Pathology</b>	124:15 126:8
253:15 255:2	216:24 238:4	325:9,15,16	174:22	127:19 130:22
256:24 263:4	239:14 241:9	326:4 330:19	<b>pathway</b> 382:21	135:18 136:12
281:2,3 282:4	243:9 244:15	331:14 371:20	<b>pathways</b>	149:3 150:16
282:9 289:12	254:12 257:23	<b>particular</b> 15:19	319:19	152:4,9 159:6
289:17 290:2	257:24 263:15	31:18 35:10	<b>patience</b> 117:2	165:15 166:19
293:17 294:9	267:6,22 268:8	40:7 46:13	<b>patient</b> 6:9	166:20,20,22
301:19 307:3	269:21 270:15	47:4 55:16	197:7 198:24	169:6 171:11
308:4,14,23	294:8,14,16	57:10 59:6	199:23	176:1 177:8
309:11 322:1	296:21 328:3	65:10 73:15	<b>patients</b> 162:17	178:9 179:3,14
323:20 326:13	352:13 365:15	96:7 101:17	182:18 189:24	179:24 180:19
326:24 328:2	366:12 421:22	118:1,16	<b>pause</b> 220:15	184:11,18
330:7 334:22	<b>particle</b> 92:4	137:11 150:19	221:11 304:7	189:23 192:6
338:1,13	108:5 136:17	151:1 153:19	<b>PC</b> 2:8	194:9 195:23
350:12 352:4	139:17 142:7	154:12,22	<b>PDQ</b> 198:9,12	206:16 209:10



211:13 212:18 214:18 228:7 232:9 233:10 233:14 241:15 242:12 245:12 246:18 248:22 260:16 265:23 275:23 293:20 304:16 326:14 332:13 333:10 333:16 343:14 345:15 378:23 381:16 390:17 403:19 426:18 <b>perineally</b> 29:13 57:14 136:24 139:14 244:9 245:4 264:20 268:19 343:13 382:17 <b>perineum</b> 88:16 166:20,21 167:2,15 175:7 175:24 176:21 179:2 199:13 213:15,21 215:12 228:5 228:24 244:18 333:24 <b>period</b> 99:3 149:6 169:11 265:15 352:15 359:7 392:7 <b>peritoneal</b> 165:4 168:9 228:6 229:1 <b>peritoneum</b> 228:10 326:17 <b>PERRY</b> 432:2 432:18 <b>persist</b> 325:1 <b>person</b> 101:24 <b>personal</b> 3:15 34:17 37:7,13 38:7,21 39:15 39:18,22 40:12 41:3 42:5,17	42:24 43:4,12 44:15 57:22 218:19,20 220:19 221:2 222:5 250:9 269:17 270:16 281:16 283:6 294:5 304:11 328:14 342:22 <b>personally</b> 33:21 34:15 57:24 261:16 <b>persons</b> 101:4 <b>perspective</b> 13:11 15:23 16:15 49:11 56:2 59:22 91:17 132:6 315:12 <b>pertained</b> 33:14 <b>Pervasive</b> 420:14 <b>petition</b> 231:9 231:10 234:13 <b>petitions</b> 232:23 <b>ph</b> 1:23 <b>Ph.D</b> 1:15 4:6 5:1 8:11,17 98:18 99:16 289:9 295:15 296:9 320:7 341:19 342:1 383:14 432:4 435:4,12 <b>Phagocy</b> 316:13 <b>phagocytes</b> 323:21 <b>phagocytize</b> 315:24 316:14 316:17 317:3 322:15 <b>phagocytosis</b> 395:3,21 <b>pharmacokin...</b> 406:24 <b>Phillips</b> 84:8 <b>photographic</b>	253:23 405:9 <b>photographs</b> 161:6 <b>phrase</b> 282:17 344:20,24 345:12 385:19 <b>physical</b> 18:20 19:18 23:15 <b>physiological</b> 396:12 <b>physiology</b> 130:3 132:12 397:18,20 406:20 410:17 <b>pick</b> 315:3 364:5 <b>piece</b> 275:2,15 423:4,5,14 <b>pin</b> 38:15 <b>piqued</b> 43:18 44:9,19 45:5 <b>place</b> 8:8 136:10 281:1 338:22 369:8 432:8 <b>placed</b> 158:22 192:3 214:14 <b>places</b> 32:5 418:4 <b>placing</b> 191:2 <b>plaintiffs</b> 13:18 <b>Plaintiffs'</b> 2:6,11 2:16 <b>platforms</b> 98:24 <b>plausibility</b> 86:23 87:1,7 87:16,22,23 90:11,12 112:20 114:12 114:17 115:18 115:19 116:1 119:6 204:4,9 204:11,16 206:8,15 207:5 207:8,10,13,14 207:22 212:20 214:1 224:9,13 234:8 236:6,18 237:24 238:24	239:14 243:4 244:16 245:8 305:6,7,10 333:13 <b>plausible</b> 112:8 112:24 228:7 232:13,15 234:10,22 235:2 238:1 326:14 330:18 331:14 336:19 337:4,14 <b>play</b> 63:1 98:1 132:13 298:14 313:10,19 314:3 321:16 388:5 <b>plays</b> 24:24 <b>please</b> 31:14 55:21 74:14 134:17 217:4 223:14 306:21 307:4 347:1 380:1 409:11 422:10 433:3,8 <b>pledge</b> 124:3 <b>plumber</b> 131:20 131:24 297:4 <b>plumbing</b> 131:16 297:2,3 297:3 <b>Plunkett</b> 110:2 142:5 185:16 185:19 186:14 186:18,23 187:11 303:7 303:19 387:1 389:22 390:9 390:20,22,23 391:6,8,14 392:3,7,9,13 <b>Plunkett's</b> 107:12 108:2,4 109:14 124:14 135:11,17 136:16 185:20 186:5 386:20	387:6 388:14 388:17 390:19 391:15 393:1 394:24 395:1 <b>pocket</b> 201:13 <b>point</b> 39:23 40:14 44:4 66:14 115:4 118:24 120:5 123:19 165:19 175:17 180:4 181:4,16 184:23,23 186:22 262:3 267:20 274:2 290:4 295:21 297:12 359:20 391:3 <b>pointed</b> 173:1 <b>points</b> 125:10 127:10 128:9 256:5 269:8 <b>poison</b> 24:23 387:17 <b>poisons</b> 5:8 20:3 24:11 <b>policy</b> 421:2 422:6,21 <b>popular</b> 84:10 <b>population</b> 418:1 <b>portion</b> 125:8 126:1 135:23 136:1,21 203:22 206:18 236:19 287:22 338:4 <b>posed</b> 27:16 28:16 <b>position</b> 67:6 84:23 99:11 229:23 236:5 264:9 276:24 281:20 330:24 331:11 421:6 422:22 <b>positions</b> 96:24
--	---	--	--	---

<b>positive</b> 367:4 367:19 368:14 368:23	16:2,10,24 17:6 27:4,20 29:13,20 30:11	242:18 244:8 244:22 245:3 246:19,24	53:14 <b>pre</b> 417:2 <b>precede</b> 402:11	98:4,10 100:17 <b>presented</b> 56:16 141:14 182:8
<b>possessing</b> 129:19	30:16,20 31:6 31:10,19 32:1	248:23 250:4 260:2,17	<b>Precisely</b> 307:24 <b>preclinical</b> 281:21	188:7 190:8,12 235:23 236:1 305:1 308:9
<b>possession</b> 67:22	32:13 33:14	264:20 265:24	<b>predisposing</b> 163:23	352:20 384:17 424:22
<b>possibility</b> 116:19 145:12 163:22 345:20	34:18,24,24 35:11 36:5,8,9 36:15,18,21	268:18 275:23 285:14 287:16 287:19 291:2	<b>prefer</b> 144:15 324:9	<b>presents</b> 52:5 257:17
<b>possible</b> 149:5 191:11 194:12 194:18,24 205:7 217:5 299:17,18,18 299:18 312:23	37:6,7 38:22 40:17 41:6 42:7,12,22 43:1,11 45:1,9 46:13 48:24 53:21 57:7,13	291:15 292:9 292:16 303:16 305:4 306:3,18 330:12 333:24 343:12,15 344:18,22	<b>preliminary</b> 163:14 399:15 401:20 413:19 <b>premise</b> 163:8 165:12 408:15 409:3	<b>prevent</b> 22:10 25:7 46:2,11 51:3 <b>prevention</b> 6:8 23:17 24:5,15 24:17 25:6 197:6
<b>post</b> 417:2	61:18,24 62:12	345:3,16 365:7	<b>preparation</b> 107:2 286:21	
<b>posterior</b> 158:22 159:8	62:16,21 65:20 66:8,18 67:8 68:8 88:16,19	365:9,14,24 366:21 367:2 368:3,21	<b>prepared</b> 276:17 285:3,6 286:20	<b>previous</b> 5:5 12:4 35:15 264:5 272:21 294:10
<b>postscript</b> 264:4 272:20 279:13	88:20 89:2,9 89:22 90:3	370:15,21 371:4 372:20	<b>preparing</b> 54:10 105:7 347:4	<b>previously</b> 9:20 30:19 33:17 34:18 36:20 55:13 151:6 178:7,8 188:22 197:11 200:11 206:2 226:24 233:7 234:4 237:3,4 245:6 252:3 260:24 264:17 265:21 283:10 294:3 300:9 307:20 314:14 315:18 325:9 327:1,10 328:13 329:21 331:19 332:23 340:4 343:10 360:1 369:21 370:11 372:24 374:15 387:8 392:23 395:15 403:18 406:16 406:19 411:12 420:1 423:1
<b>postscriptum</b> 262:23	91:3,5 95:16 108:13 109:4 110:10,15,19 110:24 111:4,8 111:13,16,22 112:6,14,15 113:20 114:8 116:7 120:10 120:11 122:6 123:8 126:7 127:18 130:23 136:12 139:13 153:18 166:24 171:12 173:4 173:17 177:9 178:10,11 180:20 184:19 192:7 199:13 212:18 213:8 213:14,20 214:4,8 215:11 216:17 226:2 229:17 232:9 232:14 233:15 233:20 236:11 241:16 242:13	374:9,12,14,19 375:8 376:9,14 376:19 377:12 377:12,14 378:23 379:9 380:5,6 381:2 381:5,11,16,19 382:6,9,10,14 382:15,17,21 403:19 411:16 412:10 424:1,7 424:7,10,12,16 424:18,20,24 425:3,5 426:16 426:21 427:7 427:16 428:7 428:16,22,23 429:13 430:1 430:10,10,17 <b>powdered</b> 173:3 <b>powders</b> 290:13 <b>practice</b> 38:17 39:18 77:23 295:15 316:16 <b>practices</b> 1:5 52:3 53:3,10	<b>present</b> 3:17 49:4 53:20 56:3 117:13 246:21 248:17 290:20 328:9 349:10 355:8 374:22 381:4 381:18 382:15 424:8,12,12,16 424:20 425:4 <b>presentation</b>	
<b>potential</b> 14:9 17:14 19:2,7 24:1 25:1 30:11 56:2 130:8 138:19 148:22 149:9 152:12 156:22 177:9 195:13 212:17 213:11 218:13 220:21 222:20 228:4 228:23 233:10 248:24 295:7 295:12 333:9 334:9 343:23 381:15 382:16 390:17 411:15 414:9				
<b>potentially</b> 22:11 46:3,11 46:12 173:4 338:19				
<b>powder</b> 1:4 8:10 9:4 11:15,21 15:10,17,20,22				

424:5	307:8,16	35:11,11,13,16	33:9 34:7	69:1,4,21 70:4
<b>primarily</b>	309:19 310:6	35:20 36:2,6	51:19 57:4	70:11,19 94:24
393:15	313:13 316:3	36:21,24 37:9	92:22 95:16,24	98:2 103:18
<b>primary</b> 21:20	316:13,24	38:22 40:17	96:15 97:9	104:3,9 106:17
163:12 287:11	317:4 324:15	41:6 43:1,11	99:24 102:2	114:23 216:9
<b>principle</b> 154:23	328:21 329:19	45:1 48:10,24	120:4 196:19	216:13 256:5
156:14,15	334:21 335:3	49:4 51:22	241:12 262:3	286:9 287:13
407:8,18	336:8 340:6	52:5,13 53:21	275:7 344:21	304:14 312:7
<b>principles</b> 21:8	<b>processed</b>	53:21 54:2,4	384:4	348:21 354:3
21:12,16 22:2	289:22	57:7 61:18	<b>projects</b> 312:11	392:4
408:11,23	<b>processes</b> 49:9	62:1,13,16	<b>promise</b> 373:12	<b>provides</b> 73:20
409:13,15	389:10	65:21 66:8,18	<b>promised</b>	353:16 354:16
<b>print</b> 40:10	<b>processing</b>	67:8 68:8	147:13	356:16 357:6
197:17 220:7	291:14	127:18 216:17	<b>promotion</b>	360:1
<b>printout</b> 386:6	<b>produce</b> 259:3	225:15,21	335:17 336:13	<b>proximity</b> 88:1
<b>prior</b> 32:24 33:5	337:5	250:5 263:8	<b>pronounce</b>	88:12,20 89:14
39:23 148:20	<b>produced</b> 69:13	264:13 272:13	218:24	90:19
165:1 177:22	388:23 389:4	274:10 276:11	<b>pronunciation</b>	<b>PTI</b> 3:10,10
416:15 417:12	408:13 409:1	281:22 287:17	172:14,17	<b>public</b> 1:21 66:8
432:3	<b>product</b> 15:1,5,9	290:12 292:16	<b>proof</b> 226:13	220:1 432:3,21
<b>probably</b> 92:24	27:4,10 31:3	316:23 342:2	230:24	435:20
96:16 119:22	32:4 37:6,7	344:19,22	<b>proper</b> 227:21	<b>publication</b> 5:11
124:6 175:21	46:13 48:24	345:4 350:14	430:1,5	5:19,21,22 6:3
215:18 249:22	51:1,4 54:1,1,9	352:9 365:14	<b>properly</b> 138:13	6:4,6,7,12,14
255:20 258:23	54:12 55:4,5	366:1 370:22	408:14 409:2	6:20 7:11
275:9 298:2	55:16 56:1,3	371:4 376:14	409:10,19	64:18 72:11
321:19 324:9	56:10,14,17	377:12 379:9	410:5	157:21 159:20
429:21	111:14 219:9	380:5 382:10	<b>proposed</b> 82:23	164:13 166:16
<b>problem</b> 194:2	287:18 289:21	382:21 412:11	88:3 90:13,20	170:14 172:9
281:11 420:14	290:5 291:5	424:1,7,10	91:4 305:3,12	174:17 217:16
<b>proceed</b> 86:16	292:4 305:20	425:1,3 426:21	305:14,22	220:2 249:11
147:22 240:13	345:5 352:1	427:7 428:8,12	306:8 307:6,14	302:22 320:18
284:8 364:16	357:9 360:5	428:13,22,23	309:17 310:4	415:10
<b>proceeding</b>	362:8 374:19	430:17	<b>propounded</b>	<b>publications</b>
155:12	374:20 380:13	<b>professional</b>	435:6	64:15 179:13
<b>Proceedings</b> 4:3	380:17,24	33:13 48:22	<b>prove</b> 79:5,10	256:4 320:8
8:1 431:22	414:10 429:13	432:18	79:10,13,17	<b>published</b> 65:14
<b>process</b> 49:8	429:13	<b>professors</b> 385:8	<b>proved</b> 193:7	83:12 118:8
98:17 118:21	<b>products</b> 1:4,5	<b>program</b> 222:17	<b>provide</b> 27:8	173:22 174:21
119:1,12	3:15 9:4 11:15	384:21 385:5	74:1 76:8 85:7	182:13 183:22
121:21 155:13	15:10,22 16:2	385:11,11,16	126:2 131:12	218:3 219:22
164:10 268:7	16:18 17:2,6	386:1 404:24	229:5 237:15	294:12 302:23
268:24 269:3	17:13 24:13	<b>progress</b> 228:12	278:4 355:1,6	303:2 419:16
269:22 270:15	30:16,21 31:6	326:19	358:4 388:16	<b>PubMed</b> 39:1,7
291:11,17,24	31:10,10,18,19	<b>progressive</b>	<b>provided</b> 34:6	40:11 63:12
291:24 292:2	32:10,14 33:14	400:10 402:1	51:9 55:7 63:5	64:7 70:24
305:24 306:10	34:15 35:1,9	<b>project</b> 31:9,17	63:9 68:5,13	178:17 252:1

<b>pull</b> 70:22 76:7 144:8,9 145:14	409:6,10,17	349:13,19	421:5	42:23 108:13
<b>pulled</b> 163:7	<b>puts</b> 56:6 180:4	351:21,22	<b>quoted</b> 25:21	109:5 110:12
179:12 191:11	<hr/> <b>Q</b> <hr/>	352:18 356:8	145:11 181:15	130:23 199:14
391:13	<b>qua</b> 74:12 77:19	360:7 361:13	185:6,8 186:23	232:5 266:9
<b>Pump</b> 13:6,7,8	80:7	365:1 377:22	189:5 232:19	333:16
13:10,15,19	<b>qualifications</b>	380:1 394:6	235:12 290:6	<b>reached</b> 199:20
<b>Pumps</b> 13:4	289:7 384:18	395:5 398:5	334:21 417:4	364:15 418:12
<b>punctuation</b>	423:17	417:7	<b>quotes</b> 69:1	<b>reaches</b> 228:8
98:15 100:18	<b>qualified</b> 289:1	<b>questionable</b>	142:18 218:9,9	326:15
<b>purchasing</b>	408:14 409:2	279:16	223:5 224:11	<b>reaching</b> 175:10
429:9	409:20 410:5	<b>questioning</b>	253:9 263:17	176:4 334:3
<b>purporting</b>	<b>qualitative</b>	205:3	<b>quoting</b> 179:20	<b>react</b> 85:12
248:6	405:23 406:12	<b>questions</b> 9:23	310:1	<b>reaction</b> 228:11
<b>purpose</b> 11:4	407:5	10:3,7 25:4	<hr/> <b>R</b> <hr/>	326:18 327:3,6
21:20 29:4	<b>question</b> 9:24	52:11 117:2	<b>R</b> 2:1,2 3:1	328:10
41:2 170:5	10:8,12 19:5	146:19,22	198:13,15	<b>reactions</b> 317:22
287:11	19:12 27:14,15	160:19 198:20	<b>R-A-D-I-C</b>	<b>reactive</b> 324:2,4
<b>purposeful</b>	28:1,3,16	215:17 248:18	389:21	324:8,13
10:13,17	31:14 35:23	285:16 397:2	<b>R-E-I-L-L-Y</b>	<b>read</b> 18:21,22
245:14	36:1 55:18	423:22 431:18	99:10	19:13 22:9,13
<b>purposes</b> 93:18	56:12 58:23	435:6	<b>R.P</b> 341:19	22:14,19 23:4
150:7 250:10	65:5,10,19	<b>quick</b> 86:7 280:9	<b>Radic</b> 389:21	23:12 25:10
286:14 287:20	67:9 114:20	338:20	390:9,12 391:8	39:19 43:24
292:6 374:9	121:5,9 122:2	<b>quite</b> 56:19	392:14	46:18 51:11
430:24	122:10 134:2	185:15	<b>raise</b> 283:1	74:17 76:1,11
<b>pursuant</b> 432:10	134:14 138:12	<b>quotation</b> 147:7	<b>range</b> 21:10,11	84:1 88:4,6
<b>pursue</b> 342:12	146:15 147:12	151:21 187:17	49:15 64:10	103:19,22
<b>put</b> 18:15 22:8	150:4,4 194:18	272:17	138:18	104:5 107:18
28:2 42:2 51:9	196:15,16	<b>quotations</b> 78:4	<b>rate</b> 97:6 101:15	135:14,23
59:11 64:12	197:15 198:1	145:24 263:24	101:20,22	136:1 148:16
71:18 78:4,8	209:13 220:15	<b>quote</b> 68:24	102:6 276:15	148:17 149:12
88:19 101:15	224:3 240:20	76:11,21,23	<b>rates</b> 102:10	152:20,21
126:11,23	241:20,21	77:4,10,15	<b>ratio</b> 294:20,22	163:19 168:19
139:11 146:1	242:9,10	87:23 124:14	296:7 298:24	169:2 170:2
154:7 177:15	243:21 244:7	142:2,15,15	299:4,20	171:17 173:7,9
184:13 192:15	245:2,15	144:1,5,9	300:14,16,22	176:6 177:3,13
194:23 200:16	246:13,17	146:13 148:5	<b>ratios</b> 294:24	178:22 179:11
203:22 211:20	247:12 248:22	149:3 170:22	295:6,18,23	182:15 192:2
216:12 229:12	254:10 259:22	175:11 181:13	296:16,18,19	193:13 196:8
229:18 231:5	260:16 268:23	185:2 187:7,8	297:7,17,21	197:23 205:11
238:4 267:2,15	274:2 277:20	199:16 218:7,8	298:1,8 300:6	205:14,19
268:5 270:13	292:23 297:20	223:6,24 236:4	300:18 301:13	206:1,4,18
290:23 311:23	310:7 329:4	238:14 239:20	<b>rats</b> 400:13	207:4,6,14,22
323:2 351:10	331:6,18 337:4	243:20 263:2	402:4 410:21	218:1,16,18
354:19 360:5	343:3 346:15	282:15 289:18	<b>RDR</b> 432:18	220:6 228:20
370:4 399:9	346:19 347:1	369:13,15	<b>reach</b> 41:17	234:24 253:12
		392:6 406:3		253:13,21

254:15 258:22	318:24 424:4	141:13 150:6	221:17 223:11	37:14 144:21
263:9,14	<b>realtime</b> 1:20	173:21 197:16	231:15 235:19	149:8 155:12
273:16 274:5	145:7 432:2,19	198:4,9 201:23	238:10 240:1	160:5 179:12
304:15 307:2	<b>reason</b> 9:24	203:19 225:6	252:19 255:14	182:4 188:1
309:3 320:14	158:12 177:21	225:12 245:21	298:2 303:13	191:9 217:6
326:22 352:8	258:7 290:14	249:3 283:17	305:10 324:10	222:9 273:5,9
390:19 400:15	354:13,21	293:12 302:1	346:13 417:19	283:9 287:19
400:16,22	359:18 433:5	318:21 320:22	418:20,22	290:1 293:24
405:8 407:4	434:4,6,8,10	341:21 362:23	419:1 426:11	312:6
422:8 429:16	434:12,14,16	408:22 409:16	<b>reference</b> 5:6	<b>references</b> 10:24
433:3 435:4	434:18,20,22	419:17	13:10 17:18,24	70:21 71:5
<b>reading</b> 23:7	434:24	<b>recognized</b>	18:2,6 19:14	83:11 100:4
45:20 53:13	<b>reasons</b> 65:8	60:13 74:21	20:14 24:9	144:24 151:1,9
163:6 169:1	193:6 279:16	84:7 148:4	70:13 71:11,17	151:15 154:13
217:24 263:14	317:10	297:10	71:18 73:4	158:2,9 180:12
401:2 421:11	<b>REATH</b> 3:2	<b>recollection</b>	82:19,22	182:11 188:9
<b>reads</b> 77:4 282:9	<b>REBECCA</b> 3:12	82:9	102:16 105:23	189:1,13,14
<b>Readwin</b> 13:3	<b>recall</b> 13:24 15:3	<b>recommend</b>	106:1 124:24	191:14,19
<b>ready</b> 86:16	15:8 45:3 46:5	301:20	126:3 127:4,6	192:13,14,15
147:22 240:12	46:7 55:9	<b>record</b> 8:4,13	143:2,8 144:6	192:19 195:9
284:7 364:16	81:19 106:20	49:21 86:7,9	145:3 154:8,22	199:24 203:11
<b>real</b> 258:17	123:15 181:12	86:13 102:17	158:7 160:18	208:9 222:3
263:7 264:12	190:11 196:23	147:11,15,19	164:7,18	230:6 231:6,14
272:12 278:12	202:15 207:19	240:6,10 284:1	168:22 183:12	255:9,13,16,21
279:8 282:14	259:17 283:19	284:5 307:4	183:24 186:18	256:14,23
384:12	287:14 313:15	322:6 340:18	189:2 190:4	257:8 302:7,11
<b>realize</b> 35:24	316:18 368:2	359:10 361:8	191:4 193:1,9	327:12 338:19
411:8	384:22 387:7	363:7,14 364:8	194:12,23	352:3 354:13
<b>really</b> 31:7	405:15	364:12 395:1	202:3,19 205:5	358:19 387:6
34:22 35:7	<b>receipt</b> 433:16	431:1,13,21	205:22 216:23	391:15 392:17
38:18 40:20	<b>receive</b> 106:15	<b>red</b> 283:1	251:9,11,20	392:18
41:20 48:1	289:4 419:21	<b>redacted</b> 96:10	252:10 256:12	<b>referencing</b>
52:23 62:23	419:22,23	101:9,12,12	283:8 290:15	150:18 247:10
85:10 90:12	<b>received</b> 20:16	<b>refamiliarize</b>	291:13 351:24	293:17 426:17
98:8 100:20	22:20 69:9	190:24 252:17	352:22 353:24	<b>referred</b> 12:1
120:14 154:6	104:7,8	347:7 405:3	354:7 359:19	60:6 127:8
155:10,14	<b>receives</b> 419:24	<b>refer</b> 22:3,3 58:1	363:24 366:17	128:2 205:24
166:3 170:21	<b>Recess</b> 86:10	60:5 74:13	366:20 389:17	256:12
179:18 202:22	147:16 240:7	90:4 117:10,11	389:18 390:1	<b>referring</b> 18:18
241:21 257:21	284:2 364:9	123:11 127:14	390:21 391:13	31:5 33:7
264:6 273:6	<b>recessed</b> 431:22	131:11 133:3	392:8 395:7	88:14 100:21
302:20 324:7	<b>recognize</b> 12:9	134:3,9,19	398:22 402:19	108:12 143:8
339:1,1 340:23	18:3 20:10	135:1,2 143:1	405:14,20	149:19 166:23
348:11 349:8	25:9,16,24	144:7 151:3,10	410:8 415:14	186:14 204:23
349:18 356:2,8	26:13 57:16	166:22 182:10	415:18,20	211:18 222:14
<b>realm</b> 113:15	72:14 74:15	211:6 215:18	<b>referenced</b>	222:19 238:14
138:21 213:8	103:1 119:10	215:24 216:4	26:20 28:14	282:23 289:16



323:16 327:5 328:16 335:17 344:10 355:5 383:20 <b>refers</b> 294:19 305:12 321:20 328:14 388:16 <b>reflected</b> 288:20 <b>refreshed</b> 313:14 <b>refresher</b> 318:8 <b>refreshing</b> 314:4 <b>refute</b> 281:12 <b>regarding</b> 9:15 22:2 27:19 29:11 30:10 32:1 35:15 42:22 44:21,24 45:8 49:17 51:12 52:13 53:14 54:2 55:11 56:7,21 56:24 57:11 59:12 60:2 62:19 66:22,24 67:3 76:5 78:12 85:2 91:2 95:1 114:16 127:10 130:20 132:16 137:13,20 163:4 211:5,8 213:4 216:16 224:12 225:21 227:7,24 231:8 236:10 237:12 238:21 245:3 248:22 261:1,2 261:3,6 275:21 278:5 285:13 287:16,22 292:11 298:1 306:3,17,18 308:14 319:20 324:11 334:15 334:20 338:9 343:11 352:4	354:19 355:1 356:17 357:10 362:5 364:24 365:9 366:21 370:15 371:12 371:18 372:20 373:3 374:14 377:9 378:6,22 379:1 381:2 382:13 387:7 389:14 390:16 391:1,18 393:6 394:4 404:4 417:20 419:3 426:13,14 430:18 <b>regardless</b> 33:13 183:20 202:16 234:6 272:23 298:24 <b>regards</b> 15:2 16:7 17:4 30:19 31:22 34:18 41:24 42:11 49:13 54:1 56:5 58:13 110:3 112:1 121:13 126:3 150:12 155:7 225:20 244:21 258:20 286:12 287:7 288:11 295:6 295:16 326:4 330:11 332:6 332:24 337:14 339:18 354:1 355:3,7 358:6 365:6 366:4 368:13 372:17 406:17 424:4 426:4 <b>region</b> 321:9 <b>regions</b> 404:9 <b>registered</b> 1:19 198:16,17,21 198:22 432:2	432:19 <b>regular</b> 39:20 <b>regularly</b> 27:10 <b>regulation</b> 50:13 400:11 402:2 402:16 <b>regulations</b> 49:17 50:14,17 50:20 51:12 52:12,24 53:13 53:14,16 54:2 57:23 59:11,12 60:8 225:22 <b>regulatory</b> 49:12,16 52:22 53:8,9 58:13 208:6 <b>Reilly</b> 99:8,18 <b>reiterate</b> 114:5 <b>related</b> 12:18 33:8 104:4 163:22 307:10 310:13 342:8 426:15 <b>RELATES</b> 1:7 <b>relating</b> 343:23 <b>relation</b> 90:24 125:12 365:23 <b>relationship</b> 11:14 27:3 29:19 33:1 65:19 68:7 87:2,24 90:13 119:13 122:5 194:9 226:21 226:21 245:12 246:24 265:2 265:14 295:12 299:21 381:15 385:24 403:23 415:4 416:3 <b>relationships</b> 295:8,17 300:2 <b>relative</b> 432:13 432:14 <b>release</b> 12:13,19 323:22 324:2	<b>releases</b> 312:6 <b>relevance</b> 137:7 339:13 <b>relevant</b> 64:24 65:18 181:8 196:5 214:7 240:18 299:4 343:5 365:2 <b>reliance</b> 21:23 <b>relied</b> 68:15 216:12 238:5 253:17 289:12 <b>relies</b> 88:1 90:11 90:13,22,22 <b>rely</b> 42:5 145:10 145:13 191:19 215:22 255:5 366:11 392:18 405:24 407:6 <b>relying</b> 71:20 <b>remains</b> 223:8 224:1 259:20 <b>remember</b> 32:21 42:20 44:4 97:18,20 143:17 181:19 231:9 253:24 280:14 320:7 321:18 355:21 405:10 410:1 420:11 429:20 429:21 430:12 430:14 <b>remind</b> 259:11 <b>remove</b> 289:23 325:14 <b>removed</b> 325:17 <b>removing</b> 140:19 <b>rendered</b> 376:3 390:13 <b>renders</b> 350:13 352:1,9 <b>repeat</b> 122:1 309:21 346:24 380:1 426:23 <b>repeatedly</b>	279:17 <b>rephrase</b> 194:17 311:20 <b>report</b> 5:4 6:18 9:7,14 10:12 10:24 11:7 18:1 20:24 22:2 26:13 27:22,23 28:6 28:11,21 29:3 29:5 30:2 32:5 32:8 58:11 68:14,18 69:15 69:22 71:6,12 71:24 72:2,21 73:1,17 76:18 76:22 77:8,9 77:12 78:3 83:19 87:1,15 87:21 88:9,24 89:7,19,20 90:5 96:19 98:3,5,12 100:12,16 104:15 105:1,8 105:11,13,20 106:2,4,8 107:12,19 108:10,11 109:3,18 112:19 116:4 117:4 120:5 124:14,21 129:3,7 132:18 132:19 133:16 133:17,18 136:5 137:6 140:11,18 141:16,24 142:6,13,16 144:6 145:11 146:1 147:8 148:5 151:21 153:17 155:6 156:9 158:3,5 162:9 165:21 168:3 177:19
--	---	--	---	--

181:14,16	351:24 352:23	290:20	141:21 211:19	383:22 384:1
183:18 184:3	354:23 355:18	<b>representatives</b>	234:14 237:13	384:12 389:9
184:10,21	357:15,18	61:10,13	254:17 271:4,4	<b>responses</b> 317:2
185:2,7,9,11	358:18,20	<b>Reproduction</b>	291:16 295:17	317:22 319:15
185:15,21	359:2 366:15	174:1 218:4,5	296:9 302:20	<b>rest</b> 77:7 279:22
187:4 188:22	366:18,22	<b>reproductive</b>	306:14,17,18	308:23 406:6,7
189:3,14	367:6 368:2	89:24 91:7	315:7 318:16	<b>restate</b> 95:19
190:18 191:3	372:18 373:6	108:15 109:6	319:17 324:21	<b>restricted</b>
191:10 192:10	373:21 379:17	110:11,20	332:4 340:5	198:13,16
192:14,16,20	379:18 380:23	111:5,10,18,23	342:23 372:18	<b>result</b> 417:5
196:9 200:19	383:4 384:17	116:9 120:12	375:10 378:4	420:24 422:19
202:19 204:10	384:17,24	135:21 137:14	378:11 387:20	<b>resulting</b> 14:10
204:20 205:6	386:20,21	148:14,23	388:6 393:11	<b>results</b> 282:12
205:11,24	387:2,3,6	149:11 152:1,6	394:10 396:17	330:20 367:5
206:5 207:21	388:14,17	152:18 195:24	400:17 405:18	368:8 399:15
208:12 210:24	389:18,23	213:22 215:13	408:2 409:22	404:15
211:4,7,15,16	390:10,11,13	232:5 260:19	411:1,19 421:1	<b>retail</b> 15:1,6
211:20 212:4	390:15,19	303:17 327:13	422:5,20 424:6	27:3 54:9
213:10 216:14	391:15,16	<b>reputable</b>	<b>researched</b>	<b>retained</b> 34:10
217:7 219:18	392:4,5,17,18	301:21	38:19 138:6,9	61:12,14
233:9 235:5	393:2,3,3,16	<b>request</b> 106:7	141:1 172:3	370:14
238:5,17 239:1	394:24 395:2,9	183:12 285:22	227:23 315:19	<b>retention</b> 27:16
240:2 245:10	398:22 399:3	289:3 431:4	339:19	33:9
251:12 252:10	404:24 405:1,3	<b>requested</b> 106:3	<b>researching</b>	<b>Retire</b> 7:12
252:17 255:22	405:9 411:5,9	288:17 432:11	138:10 340:3	419:11
256:13,14	411:22 412:10	<b>require</b> 124:16	<b>reserve</b> 304:24	<b>retrograde</b>
258:22,24	415:3,18 416:7	135:19 267:6	431:3	142:9,17 144:2
265:22 271:6	416:12,16	<b>required</b> 54:18	<b>reset</b> 114:20	147:2 148:22
278:4 284:15	417:16,19	74:11 77:18	<b>residences</b> 176:9	149:10,15
284:21 285:1	418:8 419:2	78:17,24 81:14	<b>respiratory</b>	150:2,5,13
285:12 287:23	423:23 424:5	148:15 163:16	140:2,4,7	151:13,18
289:12,18	425:23 426:17	164:2 342:14	313:19 323:5,7	152:12 156:22
290:7 302:7	<b>reported</b> 152:15	357:7 358:5,8	<b>response</b> 12:19	173:1 185:4
303:14,19	153:4 281:4	362:6	17:13 44:15,19	206:14 293:18
304:1,3,3,5,22	<b>reporter</b> 1:19,19	<b>requires</b> 299:1	228:11 234:13	<b>retrospect</b>
306:16,20	1:20 8:14	<b>resay</b> 89:12	263:2 272:19	127:16
307:19 308:1	85:22 386:8	134:15	273:2 282:7	<b>retrospective</b>
309:3,5 310:1	432:2,3,3,19	<b>research</b> 15:20	283:7 310:20	294:10
310:3 315:16	432:19,20	25:7 32:6	311:8,19	<b>return</b> 114:15
315:21 318:7	<b>Reporters</b>	34:17 37:14	312:16 313:7,9	369:4 433:14
319:16,18,23	432:18	38:4,7,22	314:2,5 316:5	<b>review</b> 11:12
330:12 333:12	<b>reports</b> 44:16,19	39:15,23 40:12	317:11,15	14:23 16:5
336:11 337:10	45:2,5 104:3	40:16 41:10	318:9,12 319:7	34:1 51:9 98:6
337:18 338:5	135:3,5 202:15	42:6,18,24	321:10,12	98:8 100:15
339:18 340:8	251:19,22,24	43:12 44:15	325:14,17,22	103:9,22
346:1,11	277:9 286:24	130:6 138:8,22	326:8,18 327:3	106:11 113:8
350:10,10	<b>represent</b>	138:23 139:3	327:6,18 330:2	113:10 115:12

116:21 117:19	304:8,21	207:17 210:21	<b>Road</b> 2:14	362:9
131:6 144:19	<b>revisited</b> 327:1	217:1 219:4,24	<b>Rock</b> 18:9	<b>sale</b> 52:5 53:20
145:14 161:19	<b>revisiting</b>	220:2,4 221:8	<b>role</b> 24:12,24	<b>SALES</b> 1:4
162:4,11	326:10	223:19 224:15	45:8 63:1 98:1	<b>Samantha</b> 63:17
165:21 171:6	<b>revolves</b> 17:5	228:20 231:22	99:18 100:23	97:1,10
173:11,19	24:11	232:22 235:12	125:22 136:9	<b>sampled</b> 290:12
176:19 178:22	<b>revolving</b>	236:21 238:20	164:20 313:10	<b>samples</b> 285:14
183:1 184:17	330:11	240:3 243:11	313:19 314:4	288:9,11,14
189:7 193:19	<b>Richard</b> 219:7	247:15 248:8	321:16 338:6	290:2,23,24
201:6 206:3	293:11	264:3 266:20	384:7 388:6	291:1 292:8,10
209:15 210:17	<b>right</b> 21:18	270:2,8 275:18	<b>roles</b> 320:11	<b>Sander</b> 81:3
210:22 221:17	23:10 26:4	277:19 278:14	<b>room</b> 266:17	<b>satisfy</b> 115:24
231:15 246:5	36:2 39:5	281:24 296:24	341:10	116:1
252:18 254:16	44:23 45:16	302:7 304:24	<b>ROS</b> 324:2	<b>save</b> 157:24
254:22 255:18	47:4 48:16,18	305:8 308:1,18	<b>Rothman</b> 81:7	<b>Saves</b> 124:8
255:21 256:2	52:24 60:11	312:4 316:15	85:11	<b>saw</b> 40:3 105:15
256:18 258:21	68:17 71:7	317:7,14 318:4	<b>Royston</b> 3:10	106:1,13,18
258:23 277:10	73:16 75:5	319:12 321:12	<b>Rudie</b> 2:2 8:23	113:17 196:18
334:15,20	76:10,19 81:21	322:1,2 323:4	10:11	202:8 327:24
349:15,19,23	82:11 85:22	323:11 331:8	<b>rudiesoileau...</b>	418:12 429:10
<b>reviewed</b> 5:16	96:3,9,22	332:9 335:6	2:3	429:21
23:9 34:2	97:22 99:11	338:1,8,10	<b>rule</b> 259:19	<b>saying</b> 76:8 92:3
41:21 55:5	100:20,24	339:21 343:3	301:5 432:10	110:7 111:1
68:14 102:21	101:14 105:23	343:20 349:18	<b>rules</b> 75:22	153:4 169:6
103:5,19 104:6	107:22 111:11	350:12,21	76:15 84:5	177:14 178:19
104:8,20	111:14 115:11	353:6 354:6	<b>run</b> 71:8 388:21	193:14 221:9
106:22 113:14	115:15 118:10	358:20 363:5	<b>rusty</b> 80:9	234:10 242:8
115:23 116:14	118:12,20	366:11 367:14	<b>rwoods@seyf...</b>	246:20 248:14
130:19 132:16	128:19 131:15	367:16 371:24	3:13	273:4 281:2
160:6 166:2	136:3 142:14	372:15 384:3		298:19,22
170:18 172:19	142:19 143:10	386:4,18	<b>S</b>	302:6 309:4,5
174:6,24	143:13 144:12	387:11 388:18	<b>s</b> 2:1 3:1 321:16	316:14 341:23
182:21 183:11	145:6,7 147:10	388:19 392:24	<b>S-H-I-M</b> 388:13	372:17 397:7
205:7,11	150:21 151:2,4	397:13 407:19	389:19	401:13 402:13
216:13 234:4	154:10,16	413:17 414:1	<b>S-J-</b> 219:1	418:18
255:7 257:16	155:9,22 156:6	414:11 418:8	<b>S-J-O-S-T-E-N</b>	<b>says</b> 18:18 23:13
258:22 285:8	156:9 163:1	420:2 424:13	172:14 293:24	25:21 50:23,24
348:20 418:7	166:21 167:8	426:2 431:3,15	<b>sacrifice</b> 399:19	68:24 75:4
<b>reviewing</b> 70:2	167:14 171:9	<b>Rigler</b> 366:23	<b>safe</b> 43:1,12	76:3 77:18
98:3 100:11,16	172:5 174:6	373:20	61:18 62:1	78:9 80:4 84:3
138:11 146:6,9	175:4 176:4	<b>ring</b> 162:12	66:18 370:21	121:4 143:1,23
162:6 194:18	179:22 180:5	<b>risk</b> 7:2 59:19	371:3 426:20	144:2 146:24
208:6 254:23	182:2 185:10	59:24 60:2,14	427:5,6	148:20 149:3
256:19 259:4	190:10,14,15	60:22,23	<b>safety</b> 40:16	149:15,20,23
267:24	190:22 193:21	199:12 257:2	41:5 54:15	151:23,24
<b>reviews</b> 63:9	195:20 198:18	293:21 348:1,6	67:8 219:9	152:11 153:8
<b>revisit</b> 220:15	202:11 207:9	430:18	354:18 360:4	158:18 161:1

161:14 162:15	24:17 27:11,18	385:2	136:22,23	270:11,13
164:19 165:2	28:6,14,22	<b>scientific</b> 11:18	137:5 138:1	271:2,9,10,12
170:22 176:22	29:10 30:8	16:6,8 17:7	139:4,12,22	272:10 274:8
180:15 182:15	31:23,24 39:3	27:11,19 28:7	145:16 150:15	275:21 276:3,9
189:24 202:23	40:22,23 41:14	28:22,23 29:10	151:11 155:19	277:6,13
219:22 223:6	41:23 42:11	29:11,18 30:8	155:24 156:10	278:11 279:7
223:18 224:9	43:19,20 44:21	30:9,10,22	160:7 161:20	283:2 296:10
228:3 230:1	44:24 56:8,22	31:24 37:18	164:9 167:23	299:5 301:16
234:18 259:12	57:2,11,12	38:24 40:5	170:3 186:10	302:19 303:6
262:22 268:14	62:5 63:22,24	41:12,22 42:10	186:19 189:19	303:14,21
273:15 276:9	64:2,6 66:21	43:7,16 44:8	191:20,20,23	304:13 305:2
278:10,16,16	67:12 80:2	44:11,14 45:6	195:9,11,22	332:10,15
279:8,13 281:3	97:19 112:11	45:11,15 46:10	199:19 200:4	333:2,14,17,23
282:7,16	113:12,17	46:16,17 56:8	209:16,20	337:12,19
293:19 294:8	114:6 117:16	56:21 57:2	210:17,23	339:22 343:11
297:9 302:17	117:24 118:18	62:6,11,11,18	211:19 212:21	343:13 345:1
321:12,14	119:18,20,23	63:2,3,7,19	213:1 215:4,9	345:13,14,16
328:2 342:7	121:3,11,14,17	64:9,13,18,22	215:10 216:5	365:9 366:19
348:6 352:24	121:17,18	64:24 65:4,18	221:3,4,15,18	372:19,22
353:3 361:9,9	122:24 129:14	65:24 66:22	222:6 229:15	374:13 376:11
369:13 384:18	132:14 133:5	67:12,16,19	230:9 231:5,15	377:10,18
400:8 402:22	135:4 145:3	68:1 70:20	231:16,24	380:16 381:2
405:23 406:22	146:7 151:9,11	77:13 88:24	232:1,7 233:1	382:13 390:16
407:18 408:10	193:15 200:13	89:21 90:6	233:13,16,18	391:17 393:10
409:9,19	223:21 233:8	91:1 92:13,14	235:21 236:9	394:9,13 403:4
412:20 413:6,7	236:10 239:18	105:18 106:11	236:12 237:13	403:6 405:14
420:16 421:18	239:22,22	106:16 108:7	238:11 239:4,8	405:20 411:13
422:11	241:2 242:11	110:5,8,9,13	239:18 241:3	411:19 417:18
<b>scenario</b> 237:9	245:11 254:23	110:17,22	241:17 243:3	417:23 419:3
245:1 311:5	260:1 261:3	111:2,7 112:2	244:10,19,24	423:6 424:9
313:2 318:17	262:11,15	112:11,12	245:5 246:23	<b>scientifically</b>
325:20	266:13,16,16	113:3,4,8,14	247:10,12,17	79:16 108:16
<b>scenarios</b> 25:3	266:23,23,23	113:15,24	248:5,11 252:2	108:23 109:9
145:9,19 169:9	267:1,16,17	114:6,11	254:2,8,13	109:13,17,22
214:17 319:2	268:3,12 269:1	115:21,24	256:3,9,15,16	127:20 269:6
323:17 377:15	269:7,19	116:5,5 117:16	256:19 258:1	270:12 271:8
<b>Schildkraut</b>	270:11 271:11	117:20 118:2,5	259:2,4 261:1	303:8 339:11
7:10 415:2,9	271:12 272:3,4	118:8,15,23	263:6 264:11	402:19
<b>Schneider</b> 6:21	272:6 274:23	119:7,11 120:8	264:18 265:5,6	<b>scientist</b> 97:11
340:15 341:19	296:5 298:12	120:17 121:21	265:11,12,13	97:17 260:6
<b>Scholar</b> 39:1,8	299:2 300:24	123:17 125:2,4	265:18,19,22	266:2
64:7 252:1	301:12 302:21	126:6 127:5,24	266:3 267:2,7	<b>scientists</b> 44:3
<b>school</b> 385:3	343:22 378:22	128:3,15 129:6	267:14,15	47:8,16 48:7
<b>science</b> 5:8	378:24 383:17	129:24 130:2	268:1,6,13,14	49:2,2 122:16
11:19,20 16:6	383:19 387:19	130:20,21	268:14,16	122:23 272:2,7
16:12,17,22	<b>sciences</b> 138:19	131:3,13	269:1,6,8,11	<b>scope</b> 52:18
20:3 22:4 24:4	262:18 384:20	132:16 133:23	269:18 270:6	212:10,14

379:11 427:19 <b>Scott</b> 97:23 <b>scratch</b> 260:7 <b>screen</b> 175:13 217:23 322:2 <b>screening</b> 6:10 201:18 349:16 <b>search</b> 116:15 124:1 178:17 193:4 338:21 391:18 <b>searches</b> 39:1,2 63:12 66:4 70:24 252:2 <b>searching</b> 64:7,7 <b>second</b> 13:2,5,6 18:16,17 25:9 25:19 124:12 125:20 135:10 161:5,9 164:23 168:7 175:5,14 180:9 187:3,9 282:4,8 301:18 350:12 369:11 405:22 421:14 <b>second-to-last</b> 222:9 <b>secondarily</b> 91:8 139:15 <b>secretion</b> 324:1 <b>section</b> 50:15,17 50:24 68:18 69:22 70:10 82:14,15 107:12,24 108:11 116:3 124:13 142:4,5 150:23 155:6 181:6 185:14 186:4 187:4 200:1,17 207:5 207:14,21 238:13,23 240:2 251:12 306:22 319:3 365:22 369:10 369:12 387:10	404:23 406:7 419:5 <b>sections</b> 143:11 161:18 185:15 <b>see</b> 12:17 16:14 18:13 20:18 25:19 28:23 35:20 40:22 41:11,12,14,22 43:19 46:16 58:24 59:11 60:7,8,17 68:21 69:2,7 70:3 73:17 74:18 75:1,2,9 75:12,17,18 82:18,19,22 83:1,3,6 85:6 87:3,16 90:18 90:20 96:9 102:6 107:22 112:11 119:1 121:3 125:1 126:10 131:16 131:16 142:11 142:12 143:22 145:8 148:9 153:3 157:12 158:5 159:1,2 160:4 164:22 165:5,21 168:4 168:11,13 171:3,4 181:24 184:20 187:20 188:10 189:14 190:4 194:2 197:21 198:11 199:7,24 200:5 200:15 201:3,4 202:23 203:2 203:13,15 204:2 213:14 214:1 215:9 217:22 223:10 228:14 234:14 241:4 250:8,14 250:22 251:1	251:13,13 252:23 262:9 262:12,13 269:7 271:19 277:12 281:1 281:14,15,18 281:23 282:5 285:15 288:2 288:19 290:18 293:16,22 294:14,16,16 295:6 300:19 302:10,10,23 307:1 309:14 321:4 322:2 326:21 333:22 341:14 342:20 346:6 350:16 350:17 363:12 364:1 369:6,16 369:18 387:3 389:11,17 395:16,17 396:4,6 399:12 404:19 405:17 405:21,22 406:4,5 409:12 419:15 420:7 420:13 423:6 423:15,16 <b>seeing</b> 42:20 121:22 150:9 184:16 231:13 271:11 394:21 404:12,14 420:11 <b>seen</b> 34:19 35:14 37:16 40:15 43:17 46:18 105:19 124:24 160:13 180:3 197:10,12 209:8 217:12 220:1 233:24 246:6 261:19 273:2 280:21 282:19,21	294:3 305:1 341:1 344:20 348:5,8,22 373:20 386:5 386:16 420:3 <b>select</b> 103:24 <b>selected</b> 239:13 <b>sells</b> 15:22 16:18 48:23 <b>seminal</b> 72:23 <b>Seminary</b> 2:14 <b>sense</b> 47:7 55:18 64:20 70:1 125:6 126:2 217:23 222:18 <b>sentence</b> 18:17 22:8 75:2 76:19 77:4,8 88:4,6,8,11 107:21 127:9 136:2 137:11 148:3,4,9,10 148:18 149:7 150:20 152:10 152:23 153:19 157:15 165:1,2 170:21 171:3 173:13 177:2 179:12,19,19 180:1,4,9 186:4 187:17 202:23 228:16 239:8 253:12 253:13,14 254:24 255:1 256:22 263:4 282:9 307:3,19 308:4,14,22 309:11,13 324:24 326:24 350:12 352:8 352:14,16,22 357:21 358:12 358:15,23 359:2,8,21 369:12 401:5 401:17 402:22	404:2 405:22 407:20 413:22 414:12,20 421:12,23 <b>sentences</b> 98:15 200:17 334:22 405:4 <b>separate</b> 26:23 67:14 138:10 290:22 <b>separated</b> 292:10 <b>separately</b> 93:6 <b>separation</b> 289:22 <b>September</b> 282:1 <b>series</b> 323:22 <b>serum</b> 342:15 <b>serve</b> 281:13 <b>services</b> 1:23 3:21 8:6 34:6 225:5 <b>session</b> 364:15 <b>set</b> 56:23 84:5 191:13 194:10 231:14 432:8 <b>seven</b> 136:14 <b>severe</b> 403:10 412:22 413:8 413:11 <b>severely</b> 107:17 108:3,7 109:15 109:23 186:6 186:11,13,16 186:17 <b>SEYFARTH</b> 3:12 <b>share</b> 351:7 396:11 <b>SHAW</b> 3:12 <b>sheer</b> 64:15 <b>sheet</b> 274:19 278:7 360:4 362:9 433:6,9 433:12,15 435:7
--	---	---	---	--



<b>sheets</b> 54:16	304:11 329:7	99:13 121:6	126:1 136:14	112:17 113:6
<b>Sherlock</b> 223:23	343:10 374:22	145:13 150:4	136:20 143:15	114:18 117:18
<b>Sherman</b> 341:24	376:20 380:18	216:21 229:22	189:11 197:18	118:19 120:1
341:24	417:24	241:24 243:24	212:19 220:7	120:13 122:3
<b>Shim</b> 388:13	<b>shows</b> 50:13	264:8 265:10	<b>smaller</b> 351:18	122:11 123:3
389:19 390:12	56:22 67:13	267:6 273:15	<b>Smith</b> 13:2	123:13,22
391:8 392:14	113:4 121:19	281:6 310:3	<b>smoking</b> 227:17	124:2,9 126:17
<b>short</b> 86:15	268:3 269:11	343:2	227:21,24	127:2 128:7,16
223:20 224:21	269:19 270:7,9	<b>Simultaneously</b>	<b>snippets</b> 163:7	130:10 131:1
362:16	271:13 272:5	323:21	<b>Society</b> 25:22	132:4 133:19
<b>short-term</b>	389:3	<b>sine</b> 74:11 77:18	26:1,3,18	134:8,12,18
342:14	<b>sic</b> 281:9 336:7	80:7	218:5	135:6 139:6
<b>shorter</b> 99:2	<b>side</b> 171:1 192:3	<b>single</b> 78:8,11	<b>Soileau</b> 2:2,2 4:7	140:1,8,21
<b>shortly</b> 388:21	<b>sides</b> 121:9	113:15 285:10	8:20,23 9:9	141:4,12
<b>show</b> 11:24	<b>sifting</b> 64:8	391:13 397:3	10:18,20,22	146:10 147:20
17:22 19:23	<b>sign</b> 433:8	401:16	11:5,9 12:7	154:2 155:2
26:6 49:18	<b>signatories</b>	<b>sink</b> 131:16	15:14 16:13	157:1,23
50:7 72:7	423:16,18	<b>Sir</b> 73:9,22	17:8,21 19:22	159:22 162:5
74:20 81:21	<b>signature</b>	75:19 76:12	20:5 21:17	164:16 166:11
93:5 102:15	432:10	77:15 78:23	25:8,15 26:11	166:18 167:13
141:5 145:18	<b>signed</b> 105:12	80:3 82:23	29:1,15,22	169:17,23
157:17 159:15	105:20 106:4,7	83:12 114:22	30:14 31:15	170:7,16
160:17 164:4	211:17 293:14	203:8	32:9 41:1 42:4	171:19 172:4
165:6 166:9	328:24 341:18	<b>sit</b> 46:21 60:20	42:15 43:9,22	172:11 173:20
170:9 172:5	423:13	66:16 67:18	44:22 45:23	174:9,19
174:12 181:17	<b>significance</b>	69:6,24 95:13	46:20 47:13,23	175:19 178:23
197:2,19 201:9	7:12 84:6	128:10 140:13	48:13 49:10,22	179:6,17
217:9 223:4	136:9 279:15	144:11 183:1	50:6 51:14	180:21 183:8
249:8 284:11	294:22 295:21	196:14 276:17	52:1,16 53:17	186:2,12 187:2
293:4 320:3,13	296:2 301:5	303:4 304:19	54:5 55:1	189:4 190:3,19
322:2 340:12	416:14 419:12	347:13 348:12	57:15 59:3	191:17 192:21
344:15 347:22	421:4	364:2 412:6	60:10 61:5,21	193:20 194:1
350:21 381:13	<b>significant</b>	<b>sites</b> 322:14	62:7,15 64:19	194:15 195:3
398:14 409:14	298:16 324:14	<b>situation</b> 317:17	65:7 66:5,11	197:1,9 199:10
419:8	337:6 342:17	<b>six</b> 87:12 403:9	67:4 68:4,16	200:6,18
<b>showed</b> 183:10	403:11 420:24	412:21	72:13 74:6	201:20 205:1
294:2 343:14	422:19	<b>sizable</b> 353:1	77:21 78:5,22	205:16 209:11
382:12	<b>signing</b> 433:10	<b>size</b> 98:13	79:8,18 81:2	210:13,19
<b>Shower</b> 32:14	<b>similar</b> 47:17	364:24	82:5 84:18	212:1,12
32:14 37:3,3	49:3 136:13	<b>Sj?sten</b> 6:5,12	85:20 86:4,14	214:23 215:2
226:2,2 382:10	282:5 288:15	172:8,13,23	89:4,16 90:17	215:21 217:20
382:10	294:10	217:16 219:2	91:23 92:9,17	219:14 220:12
<b>showing</b> 41:23	<b>simple</b> 41:4	219:15 293:18	93:14,17,22,23	221:7,19 222:7
175:13 279:14	56:20 258:17	293:24	94:5,14,19	223:3 224:14
409:13 410:7	<b>simplify</b> 258:14	<b>slightly</b> 156:20	102:23 103:11	224:23 225:1
<b>shown</b> 102:11	<b>simply</b> 23:2	<b>sludge</b> 290:24	105:6 107:7,9	225:17 226:8
169:19 176:18	48:21 67:9	<b>small</b> 125:8	108:19 109:10	226:19 229:7

230:12 231:2	330:14,23	398:1,13,20	201:10 204:22	<b>space</b> 433:6
232:21 233:23	331:7,20 332:8	400:1,3,5	209:4 217:2	<b>speak</b> 30:24
234:16 235:3	333:6,19 334:6	406:14 407:16	219:20 223:11	47:21 53:10
236:20 237:1	335:5,9,13,19	408:7 410:19	224:3 231:3	59:13 68:6
237:17 238:19	336:1,15 337:1	411:2 412:8	243:15 245:18	131:24 136:5
240:3,11 241:5	337:23 338:7	413:5,16	254:5 269:16	178:3 180:18
242:4 243:8,14	339:12,20	414:15 415:1	278:24 284:12	193:13 195:19
245:20 247:14	340:9,17 341:3	415:12 416:22	297:8 309:21	228:22 264:6
248:7 249:2,13	341:9,13 343:1	418:24 419:7	316:14 318:19	298:23 318:14
250:16 251:7	343:16 344:11	419:14 421:13	320:4 327:23	322:24 328:16
254:6 255:23	345:7,18 346:8	422:2,4 423:11	329:2 331:4	334:12 338:21
257:19 258:5	347:21 348:4	425:10,22	335:8 336:24	378:7,12 385:6
258:16 259:10	349:1,12 350:1	427:1,9,21,23	341:24 349:13	385:14 392:10
259:23 260:21	350:8 351:4,9	428:10 429:3	363:11 372:16	402:12
261:18 263:12	351:17,20	429:11,23	380:10 385:22	<b>speaking</b> 31:5
264:2,22 265:8	355:11 356:7,9	430:6,15,23	399:23 400:16	91:11 101:13
266:1,8,14,19	357:1,12 358:7	431:9,14	403:5 404:19	118:6 119:3
267:4,19	358:10,16	<b>sold</b> 15:6,18	416:10 418:24	121:12 122:22
268:20 269:12	359:15 360:11	31:10,18,19	421:9,15 422:3	133:8 137:21
269:20 270:1	360:19,21	365:15	422:7 426:23	140:16 145:1
271:14,21	361:1,5,10,16	<b>solely</b> 81:20 88:1	<b>sort</b> 72:22 98:6	153:1 156:17
272:8 273:3,14	361:18,23	90:11,13,18,22	98:7,21,23	181:24 187:13
273:24 274:4	362:18,22	90:23 237:6	125:6 181:5	195:21 285:7
275:4 276:1,7	363:10,17,22	<b>somebody</b>	204:7 262:9	296:4,6 304:15
276:22 277:18	364:13 365:13	249:22 336:9	273:20 278:12	310:22 316:21
278:8,22 280:8	365:19 367:13	<b>something's</b>	280:24 297:2	324:11 328:17
280:19,20	367:22 369:3	273:23	298:13 310:2	329:18 343:21
283:15,21	370:17 371:1,6	<b>somewhat</b>	316:24 327:5	364:19 365:5
284:6,23	371:21 372:5	160:15	351:7 387:12	384:18
286:18 288:16	372:14 373:11	<b>son</b> 36:9 42:14	<b>SOT</b> 26:19	<b>speaks</b> 124:21
291:8,18	373:14 374:5	380:7	<b>sound</b> 108:16,24	348:7
292:12 293:9	375:13,16,20	<b>soon</b> 362:19	109:9,13	<b>specialist</b> 63:11
296:11,23	376:12 377:1,5	<b>sorry</b> 25:13	201:15 408:18	63:14 97:4
297:16 298:6	377:20 378:8	31:13 35:2	412:24	<b>species</b> 291:1
298:20 299:9	378:13 379:3	48:12 49:22	<b>sounded</b> 297:2	324:2,5,9,14
301:2,17	379:14 380:2,3	58:16 74:13	<b>sounds</b> 10:5	396:5 406:1,2
303:23 306:5	380:11 381:6	75:15 79:19	144:16 266:5	407:7,8,14,15
306:12 307:23	381:20 382:1	84:19,24 91:10	266:15 283:18	<b>specific</b> 27:8
308:7,17 309:1	382:19 383:1	94:3 95:19	401:14	31:2,9,17,19
311:1,15 314:7	383:15 384:15	101:10,11	<b>source</b> 65:18	32:6 34:20
315:22 316:8	386:10,15	103:20 109:21	66:2 147:7	35:8 37:10
317:13 318:2	387:21 388:2	116:11 117:11	148:4 187:15	43:14,15 50:12
318:18 319:10	389:2,15 391:2	122:1,9 123:14	187:17 285:18	58:1 83:11
320:20 322:4,7	391:22 392:19	140:3 155:4	<b>sources</b> 41:12	119:22 126:3
323:10 324:22	393:19,24	169:21 174:4	64:8 213:12	143:2 150:10
325:23 327:20	394:5 395:19	174:10 178:7	292:14	151:23 154:6,8
328:18 329:5	396:1 397:6	198:17 201:3	<b>South</b> 2:2,20	155:7 175:21

206:24 207:8	362:3 366:13	358:2,4 360:1	411:12 417:17	43:8,17,20,23
210:5 225:22	366:16 367:11	362:7 371:11	<b>statement</b> 6:16	43:24 44:5
225:23 245:2	368:4,20	<b>standards</b> 53:9	18:24 19:13	57:1 110:6
248:22 252:19	382:24 386:3	426:1,8,11	22:16,24 23:3	200:12 208:9
283:20 286:12	391:16 392:2	<b>standing</b> 247:4	23:5,11,12,12	218:22 220:20
292:9 297:20	397:9 400:18	<b>stands</b> 117:7	23:20 25:10	221:1 222:2
316:19 318:16	402:13 412:3	121:19 199:3	51:2 52:10	233:1 257:7
324:18 352:7	420:9 429:1	262:7	84:15 85:2,7	273:20 283:7
352:16 356:13	<b>Specificity</b>	<b>starch</b> 173:1,16	90:10 136:18	<b>states</b> 1:1 78:14
357:23 368:20	203:16	428:5	145:11 147:7	78:19 80:22
390:22 411:22	<b>specifics</b> 21:13	<b>start</b> 12:24	154:11 168:11	173:13 175:6
<b>specific</b>	52:11 332:6	118:10 135:16	168:13,19,24	208:17 229:4
225:21	384:13 430:14	280:12 295:3	175:16,20,22	263:3 272:24
<b>specifically</b> 15:3	<b>specified</b> 30:23	296:15 297:6	176:8,20	291:23 321:11
15:17 17:2	<b>specify</b> 16:9,23	<b>start-off</b> 385:8	180:14 184:13	354:16 406:5
21:12 25:18	32:3 38:18	<b>started</b> 124:2	200:8 208:2	407:15,21
28:12 31:3	148:19 152:3,4	<b>starting</b> 202:22	220:10,14	410:4
36:23 38:15,16	279:12 294:4	282:7	223:5 224:8,12	<b>stating</b> 80:3
47:11 50:23	<b>spell</b> 97:13	<b>starts</b> 181:7	226:24 229:6	189:10 281:7
52:11 60:4	<b>spelled</b> 172:14	<b>state</b> 20:23	229:12,14	407:4
61:3 73:14,15	<b>spend</b> 53:12	72:24 73:22	230:7,21	<b>statistical</b> 7:12
77:9 90:5	393:9 394:8,18	88:7 108:4	231:19 236:5	84:6 297:22
97:19 101:23	411:3	111:24 123:17	237:19,20,23	298:3,5 419:11
104:5,6 106:20	<b>spent</b> 39:16,21	139:10 142:12	248:16 254:11	421:4
112:19 115:4	92:21 93:1	145:4 153:24	255:12 257:9	<b>statistically</b>
117:11 120:4	275:17 342:9	154:18 156:22	259:12,17,18	420:24 422:18
120:24 123:11	411:18	186:9 194:16	263:3,17,18	<b>statistician</b>
125:21 132:24	<b>sperm</b> 170:24	213:2 239:3	264:9 272:9,19	297:23
139:1 140:17	171:7	304:22 307:18	272:23 273:8	<b>statisticians</b>
141:2 143:17	<b>spill</b> 12:13,18	333:12 357:20	273:12 274:6,7	297:10
153:10 159:9	384:8	380:23 416:6	274:14,19	<b>stay</b> 126:13
173:24 174:3	<b>spinoff</b> 7:7	417:3,14	275:1,15	<b>staying</b> 133:9
178:4,14 185:1	385:12,20	432:21 433:5	276:19 277:10	<b>Steel</b> 55:12
190:2 192:2	386:13	<b>stated</b> 25:13	278:5,10 279:5	<b>Steering</b> 2:6,11
193:14 195:18	<b>spoke</b> 314:8	109:16,17	279:5,8 282:5	2:16
198:23 200:16	<b>spot</b> 86:6 415:17	151:13 177:7	282:7,17,23	<b>stenographic</b>
200:22 202:15	<b>spray</b> 14:17,19	200:23 208:4	290:6,14 297:1	8:13 49:20
204:16 207:7	15:4	209:5 238:7	301:20 306:7	322:5
209:15 226:6	<b>squarely</b> 180:4	239:7 241:13	307:2,13,24	<b>stenographica...</b>
245:11 255:13	<b>staff</b> 47:8,12	270:23 279:11	314:13 325:5	432:7
262:19 285:13	100:2	291:2 307:20	325:12 369:16	<b>step</b> 55:15,24
287:21 292:5	<b>stand</b> 129:1	308:12 325:8	369:18,20	103:13,14
294:7 299:15	181:5 303:24	327:11 337:10	371:3 402:8	120:15 169:15
315:9 318:15	304:4 322:8	370:11 372:24	406:9 407:4	241:9 273:7
320:7 336:10	<b>standard</b> 54:17	374:2,8,15	410:6,8 421:7	285:5 318:20
339:1 344:23	54:19 56:6,24	383:23 384:24	<b>statements</b>	331:22 335:11
347:5 353:23	354:15,15	397:17 407:11	41:13 42:1	335:21 339:7

<b>step-by-step</b> 291:11	305:22 306:8 307:5,14	394:17,17 396:2,3,9,10	403:14 404:10 406:18 408:5	100:9,13 <b>successful</b> 304:17
<b>stepping</b> 317:1	309:17 310:4 310:16 315:9	396:19,24,24 397:10,15	412:1,1,13,17 412:18 414:7	<b>sufficient</b> 91:12 210:10 317:23
<b>steps</b> 38:20 57:4 61:16 63:5	<b>studies</b> 7:9 16:8 16:10,23 32:2	398:18 407:1 409:23 410:2	415:2,13 416:2 416:18 417:8	325:9 <b>suggest</b> 102:7
290:3 291:3,5 <b>stickers</b> 50:1	32:2 65:10 114:7 131:7	410:13,14 411:14,21	425:2 <b>studying</b> 275:18	309:2 357:14 <b>suggested</b> 75:21
<b>stimulating</b> 323:24	148:21 149:8 149:20 150:10	412:5,9,10 417:15,24	342:9 <b>stuff</b> 129:15	282:11 <b>suggesting</b> 312:9
<b>stipulate</b> 361:5 361:12	150:22 151:15 152:11,15	418:2,3,8,13 418:14 419:4	303:1 317:17 <b>subcategories</b> 49:15	<b>Suite</b> 2:15 3:8 <b>summaries</b> 200:21 201:7
<b>stipulating</b> 361:2	153:5,8,10,20 153:22 154:1,5	420:23 422:17 424:17	<b>subheading</b> 87:6 87:22 420:13	208:7 235:11 238:9,16 <b>summarize</b> 231:12 368:2
<b>stop</b> 86:5 146:18 146:18,19	154:11,18 156:19 164:8	<b>study</b> 7:3,8 17:10,12 18:19	<b>subject</b> 379:22 433:10	373:5 <b>summarized</b> 28:3 132:19
147:11 283:22 420:17 422:12	166:4,5,5,6 170:5 176:17	19:2,7,17 23:14 24:1,10	<b>subjective</b> 268:9 269:2 271:17	278:4 286:11 <b>summarizes</b> 146:7
<b>stopped</b> 79:15 135:15 145:7	181:17,22 187:20,24	75:15,15 78:20 80:5 118:4,5	298:15 <b>submitted</b> 235:23 236:1	<b>summary</b> 5:14 5:15 19:13
206:20 263:13 <b>stopping</b> 124:18	189:7,12 195:14 208:22	130:1 138:21 150:12,18	288:13 <b>subpart</b> 50:23	84:15 90:14 93:9,12 96:6
<b>stops</b> 228:21 <b>straightforward</b> 359:17	209:6,8 210:2 214:14 247:9	153:3 154:9,23 154:24 156:20	51:7 242:15 243:18,22	162:14 224:8 224:12 257:6
<b>straw</b> 126:11,12 126:14,15,23	248:18,19 260:13 261:7	158:19 160:13 163:5,9 172:24	244:3 <b>Subscribed</b> 435:15	279:13 285:10 286:24 289:16
<b>Street</b> 1:16 2:4,9 2:20 3:13	279:14 282:11 282:13 294:11	174:13 176:12 176:14 182:4	212:19 <b>subsection</b> 235:10	348:6 417:19 419:2 <b>summation</b> 156:7
<b>strength</b> 203:13 227:5,13,19	294:13 300:17 306:3,23	188:1,14 196:12 200:15	<b>subsequent</b> 96:7 <b>subset</b> 104:5	<b>super</b> 262:5 <b>superior</b> 98:22 <b>supplemental</b> 5:16 69:9,13
300:5 <b>stress</b> 388:23 389:4	307:21 308:5 308:15 310:7,9	208:11,16,20 210:1 214:20	143:15,18 212:19	69:16 102:20 103:4,8,16 104:20 106:21
<b>stressed</b> 73:23 115:2,3	334:24 342:13 342:20,24	281:7 283:10 291:23 294:9	<b>subsiding</b> 325:1 <b>substance</b> 13:14	<b>substantive</b> 402:9 <b>substantive</b> 401:12,22,24
<b>strike</b> 39:13 62:8 358:8	343:9 345:24 365:12 374:17	300:16 301:5,8 301:21 327:16	14:14 122:5 159:12 165:2	<b>substances</b> 22:12 46:4 164:21 355:2
<b>strokes</b> 310:23 <b>strong</b> 41:23	374:23 377:13 377:15 381:14	343:19,22 346:1,9 348:2	435:7 <b>substantial</b> 402:9	<b>substantive</b> 402:9 <b>substantive</b> 401:12,22,24
227:7,8,10,11 227:12,13	382:6 383:13 386:19 387:1,3	383:9,16 388:12 389:3,8	<b>substantive</b> 402:9 <b>substantive</b> 401:12,22,24	<b>substantive</b> 402:9 <b>substantive</b> 401:12,22,24
<b>struck</b> 387:11 <b>structure</b> 243:20	387:8,12,18,18 387:24 388:5	389:11,19,22 390:9,11	<b>substantive</b> 402:9 <b>substantive</b> 401:12,22,24	<b>substantive</b> 402:9 <b>substantive</b> 401:12,22,24
<b>studied</b> 73:19 76:4 78:13,14	391:1,9,19,21 392:1,3 393:5	395:17 397:3 397:22 398:8	<b>substantive</b> 402:9 <b>substantive</b> 401:12,22,24	<b>substantive</b> 402:9 <b>substantive</b> 401:12,22,24
81:14,17	393:8,9,11,12 393:15 394:3	398:17,21 399:9,15 400:9	<b>substantive</b> 402:9 <b>substantive</b> 401:12,22,24	<b>substantive</b> 402:9 <b>substantive</b> 401:12,22,24
	394:10,14,15	401:12,22,24	<b>substantive</b> 402:9 <b>substantive</b> 401:12,22,24	<b>substantive</b> 402:9 <b>substantive</b> 401:12,22,24

71:19	<b>supportive</b>	347:2 351:8	208:14,20	163:11,22
<b>support</b> 41:15	46:17 233:13	377:21 380:2	<b>take</b> 28:13 61:16	169:7,9,10
41:24 43:7	<b>supports</b> 11:20	397:8 406:8	63:5 78:8,10	171:12 175:6
98:2 99:20	28:23 30:10	409:12 417:20	79:4,6,9,12,23	175:23,23
100:2 110:6	41:14 57:12	419:24 420:9	79:24 86:5,6	176:1,2,20
111:2,7 112:13	96:18 110:6,18	429:21	93:15 115:10	179:1,1,2,23
113:5,19,24	110:23 112:12	<b>surgery</b> 148:13	143:20 146:11	181:9 184:10
116:6 117:17	132:17 137:7	148:15	147:12 160:20	185:4 195:7,12
118:11,16	155:24 192:9	<b>surmised</b> 210:3	179:15 224:21	199:7,8,11,11
119:8 120:9	206:14 208:8	<b>surprise</b> 251:16	227:2 237:5	200:1 206:8,11
123:18 125:3	239:4 244:10	411:7	240:4 251:13	206:16 207:2
127:5 128:4	256:17 268:3	<b>surrounding</b>	280:7,9 283:22	208:18 209:1,6
130:22 131:4	268:15 269:7	298:4	289:14 297:8	209:17 210:4,7
136:23 137:3	271:12 275:22	<b>SUSAN</b> 432:2	362:19 363:23	210:9,14,23,23
139:13,23	277:17 300:20	432:18	364:4 386:4	211:6 212:6
150:15 180:12	372:22 394:22	<b>suspect</b> 340:23	387:3 388:19	213:6,11,12
180:14 184:18	<b>suppose</b> 82:6	<b>swear</b> 8:15	396:3 397:3	214:6 215:5
194:9 208:8	293:23	<b>sworn</b> 8:18	<b>taken</b> 57:4 86:10	218:10,14
213:1 214:2	<b>supposed</b>	432:4 435:15	136:15 142:21	222:21 226:13
215:10 218:7	103:14	<b>symptom</b> 414:8	146:3 147:16	228:7 230:11
221:22 228:19	<b>supposedly</b>	<b>synonymous</b>	151:20 180:8	230:24 233:10
229:16 230:9	107:14	109:19,24	230:4 237:19	240:17,23
230:22 231:20	<b>suppression</b>	149:16 150:7	237:20 240:7	241:7,23
232:2,8 233:17	389:23 390:3	<b>synthetic</b> 327:15	257:7,8 273:1	242:21 244:1,2
233:19 237:21	<b>sure</b> 10:3,13,16	<b>system</b> 7:4 140:4	282:12 284:2	244:12,13,17
241:18 244:20	11:4 30:5	140:7 313:19	308:1 356:19	245:15,16,22
260:17 265:1	31:16 35:6	323:5,8 327:14	364:9 423:3	245:23 246:10
265:14,23	37:1 55:22	351:13 353:4	432:7	246:20 247:3,3
266:13 267:17	69:20 70:5,15	389:24 390:4	<b>takes</b> 169:15	247:21 248:17
268:15,17	74:15 76:24	<b>systems</b> 314:9	247:18	249:1,18,21
277:17 285:4	77:1 83:21	314:11	<b>talc</b> 7:9 15:17	250:6,24 252:7
286:20 300:13	88:10 91:10		30:21 66:23	252:13,23
303:6,15,22	98:11,13,14	<b>T</b>	87:24 88:2,12	253:3 255:20
305:3 332:11	108:20 117:1	<b>T-A-H-E-R</b>	88:19 89:9,13	257:2,17 260:5
332:16 333:3,8	121:16 123:19	104:19	89:23 90:2,7,8	260:11 263:7
333:18,23	128:17 133:7	<b>table</b> 198:2	90:19 91:5,9	264:12 272:13
337:12 376:11	141:17 144:16	201:2 285:10	91:12,15	274:9 276:11
<b>supported</b> 29:12	156:1 160:16	286:15 287:2,5	107:13 112:1,3	281:5,8 289:19
29:18 43:20	165:9 167:9	287:7 288:2,5	124:16 135:19	290:1,24 291:1
62:20 96:18	176:10 188:12	289:16 368:23	141:22 142:10	291:2,11 292:3
109:17,22	213:9 228:17	416:16	142:17 143:9	292:14 293:20
114:7 193:7	252:21 259:24	<b>tables</b> 287:21	143:13,23	301:22 305:23
236:13 345:16	286:8,16 302:6	<b>Taher</b> 104:18,19	144:3 147:2	306:9,23 307:6
<b>supporting</b>	309:23 311:13	105:14,24	149:4,22 150:2	307:8,15 308:5
126:6 413:23	320:14 321:19	106:4,7 202:7	150:8 161:1,3	308:15 309:17
<b>supportion</b>	323:19 324:11	202:7,9,17,24	161:11,15	309:20 310:5,8
128:6	339:10 344:8	203:3 207:3	162:18,21	310:10 319:4



331:14 332:13	89:11,22 90:3	378:23 379:9	373:17 374:11	<b>tenet</b> 24:22
332:19,24	91:2,5 95:16	380:5 381:2,5	377:6 393:13	<b>term</b> 53:11 90:8
333:4,9,15	108:13 109:4	381:10,16,19	403:14 416:23	119:17 153:5
334:3,24	110:10,14,19	382:6,8,14,15	<b>tangled</b> 58:16	154:21 318:21
336:21 337:5	110:24 111:4,8	382:17,20	<b>target</b> 314:23	353:15,19
337:13 338:12	111:13,16,22	403:19 411:16	<b>taught</b> 295:14	390:6
339:2 340:10	112:6,14,15	412:10 424:1,6	296:9	<b>terminology</b>
342:9,16 343:4	113:20 114:8	424:7,10,12,16	<b>teach</b> 78:24	354:10
345:20 349:5	116:7 120:10	424:18,20,24	<b>teaches</b> 121:23	<b>terms</b> 287:3
364:18,22	120:11 122:5	425:3,5 426:15	<b>teaching</b> 21:1,8	296:5 323:3
365:1,16,22	123:8 126:7	426:20 427:7	21:16,19	344:14
366:8,10	127:18 130:23	428:22 429:13	<b>team</b> 47:15	<b>test</b> 289:5
371:14 383:3	136:11 139:13	430:9,16	95:16 96:17,18	366:14 367:5
387:9 388:23	153:17 166:24	<b>talk</b> 30:15 52:18	285:4 286:20	401:5
388:24 389:4,5	171:12 173:17	70:7 111:15,17	<b>technically</b>	<b>tested</b> 17:2
390:17 391:1	177:9 178:10	118:22 155:5	279:9	350:14 352:2,9
391:20 393:6	178:11 180:19	277:2,23 329:8	<b>technique</b>	376:19 398:12
394:4 398:18	184:19 192:7	336:16 339:4	162:16	<b>testified</b> 8:19
400:9,13	199:12 212:18	371:23 373:18	<b>telephone</b> 342:8	361:6
401:24 402:4	213:8,14,20	373:21 423:22	<b>tell</b> 10:1,2 48:3	<b>testify</b> 432:5
418:4 424:2	214:3,8 215:11	425:23	87:14 92:18	<b>testifying</b> 361:3
425:6,8 428:8	216:17 229:17	<b>talked</b> 30:18	94:9,23 96:17	<b>testimony</b> 5:5
428:12	232:9,14	48:20 195:16	127:4 160:16	12:5 21:21
<b>talc-containing</b>	233:15,20	214:13 216:8	164:6 167:22	52:21 107:3
428:19 429:10	236:11 241:15	237:4 243:3	184:4 217:24	145:7 194:3,14
<b>talcum</b> 1:4 8:10	242:12,18	254:7 282:5	234:3 237:24	194:17,17
9:4 11:15,21	244:8,22 245:3	300:9 301:14	258:6,7,12	196:2 258:2
15:10,16,20,22	246:19,24	328:8 334:21	268:22 276:23	263:20 303:11
16:2,10,23	248:23 250:4	344:17 372:6	287:10 321:24	329:14 357:13
17:6 27:4,20	260:2,16	408:9	346:16,18	357:19 379:12
29:12,19 30:11	264:20 265:24	<b>talking</b> 15:9	354:4 375:1	387:22 392:10
30:16,20 31:5	268:18 275:23	30:17 83:7	378:15 386:5	397:12 432:7
31:10,19 32:1	285:14 287:16	129:10,10	412:4 427:3	<b>testing</b> 31:2 49:8
33:14 34:18,24	287:18 292:4	133:12 134:20	<b>telling</b> 90:15	84:6 231:11
34:24 35:11	292:15 303:16	150:10 167:10	92:1 93:20	286:12 287:15
36:5,8,17,21	305:4 306:3,18	175:22,23,24	113:23 154:4	288:1,17,19
37:5,6 38:22	330:12 333:24	179:7,21,22	194:6 196:3	289:2 292:11
40:16 41:6	343:12,15	181:22 204:6,9	216:23 231:17	365:8 366:12
42:22 43:1,11	344:18,22	211:16 212:15	232:12,16	366:16,17,20
44:24 45:8	345:3,15 365:7	214:15 226:24	247:20 263:19	367:23 368:1,5
46:13 48:24	365:9,14	244:6,15	264:14 265:9	368:22 374:11
53:21 57:6,13	370:15,21	246:16 259:7	266:15 319:11	374:18 376:18
61:18,24 62:12	371:4 372:20	260:11 261:4	329:6 333:20	379:21 380:18
62:16,21 65:20	374:9,11,14,19	296:15 297:6	388:3	380:20 381:13
66:8,18 67:8	375:8 376:9,14	300:1 313:3	<b>tells</b> 119:2	382:11 408:12
68:8 88:16,19	376:19 377:11	316:10 327:12	<b>Temporality</b>	408:24 424:17
88:20 89:2,2,9	377:12,14	331:9 359:20	203:17	<b>testings</b> 367:12

<b>tests</b> 193:17 367:4 <b>Texas</b> 1:16 8:9 432:21 <b>text</b> 22:16 182:1 408:9 <b>textbook</b> 20:7,8 20:10,14,20,21 21:1,14 22:5 23:8,23 25:11 25:14,17 75:7 80:15,21,22 81:15,20,22 82:9,16 84:3 85:2,12,15 409:6 <b>thank</b> 79:22 110:22 123:20 160:22 162:3 207:24 223:17 240:4,15 251:15,18 280:19 284:10 322:10 346:23 363:19 400:3 <b>theory</b> 90:14 107:13 108:2,5 109:14 111:19 114:1 116:6 117:5,8,14,17 119:8 123:18 124:15 125:5 125:13 127:11 128:23 129:14 129:21 130:15 130:21 132:17 132:23 135:11 135:18 136:16 142:6 150:7 184:18 185:24 186:5,9,19 192:9 195:6,7 208:23 209:22 210:7 211:12 218:10 229:17 230:10 232:3 238:1 239:5	242:17 243:24 245:8 303:6 305:3 328:4,15 332:12,17 333:1,3,15 <b>thereof</b> 365:24 <b>thing</b> 66:2 90:21 111:12 179:21 207:15 238:3 328:7 378:5 <b>things</b> 16:9 41:11 52:14,17 63:13 69:16 98:17 100:4,18 109:19,21,24 116:13 117:4 118:15 119:21 126:5 127:23 128:21 132:13 135:3 137:17 153:20,23 178:13 195:15 211:8 213:12 220:21 224:11 225:20 233:2 247:22 271:5 297:4,24 314:2 323:5,6,7 330:4 356:21 371:16 389:9 393:2 397:1 399:3 406:22 423:2 <b>think</b> 20:23 24:8 33:2,4 35:5 38:1,3 40:13 54:3 70:21 71:1 77:14,22 78:1 95:11 100:1 104:7 107:24 111:12 122:9 123:16 124:5 127:16 128:10,22 134:2,2 137:18 139:7,11 148:20 151:17	152:24 153:12 154:3,14 158:1 160:1 172:13 177:21 181:4 182:12 185:10 186:8 193:6 197:12 198:2 198:15 202:6 211:9 212:13 215:15 220:6 222:24 224:4 231:12 232:6 235:20 240:22 249:21 257:20 259:6 270:23 271:24 275:9 280:5 289:13 295:1 298:9 302:5 320:2,6 323:2,17 330:1 330:8 332:22 335:4,17 336:8 338:4 341:9 343:18 346:10 346:21 347:8 347:11,11 349:9 354:22 358:7 363:22 364:14 365:21 368:5 375:2 379:20 380:23 383:23 384:18 391:12 402:18 411:3 417:4 418:19 420:8 420:10,11 424:3 430:13 431:3,15 <b>thinking</b> 362:20 <b>thinks</b> 67:7 <b>third</b> 5:13 13:3 13:7 22:7 81:23 82:3 125:20 148:9 148:10,18 165:1 226:11 282:9 294:9	341:17 <b>thirty</b> 433:16 <b>thorough</b> 63:20 113:7 <b>thoroughly</b> 64:13 <b>thought</b> 61:17 62:4,24 67:14 98:16 193:22 198:16 224:24 309:24 326:5 341:3 <b>thoughts</b> 67:2 122:17 <b>thousands</b> 64:9 116:19 191:24 192:23 193:4 392:1 <b>three</b> 109:24 117:4 122:12 143:11,16 182:18 184:12 189:24,24 251:19 302:11 321:1 383:6,7 423:15 <b>three-page</b> 341:18 423:3 <b>threshold</b> 420:20 422:14 <b>Thursday</b> 1:12 <b>time</b> 8:7 37:18 37:22 39:23 43:3,6 46:19 53:13 57:3 86:2 93:2 96:1 96:4,20 99:3 100:5 101:17 107:19 124:8 125:16 143:20 146:15 157:24 160:20 165:20 173:18 188:13 205:13,18 206:2 224:24 231:18 277:2 280:6,8,11	289:10 342:9 348:24 369:7 384:14 385:6 388:19,21 393:10 394:9 411:19 426:24 427:4 430:22 431:4 432:8 <b>time-wise</b> 85:21 <b>times</b> 101:12 120:18 121:7 254:8 277:7 288:18 330:2 333:21,22 361:14,15 418:5 <b>tissue</b> 91:21 92:8 161:2,13 162:17,20 206:10 209:1,7 210:16 211:1,6 212:7 244:1,2 245:16,23 246:11 247:4 247:22 252:15 253:4 260:6 281:5 310:19 311:18 317:22 328:9,10 332:20,24 403:9 425:18 <b>tissues</b> 107:16 161:16 163:6 <b>titanium</b> 141:22 143:9,12 <b>title</b> 50:14 85:5 183:3 186:4 198:12 201:8 <b>titled</b> 255:19 <b>titles</b> 96:24 <b>today</b> 8:11,14 9:1,17,23 16:3 21:19,20 26:24 31:4 34:8 35:24 46:22 52:18 60:20 66:16 67:18
---	---	--	---	---

69:6,10,24	203:19	138:15 241:10	175:8,9 176:3	<b>trigger</b> 82:9
118:21 128:10	<b>tort</b> 12:20,22	267:24 271:3	196:1 213:16	317:20,23
133:8,13	<b>touch</b> 337:10	317:7 342:17	213:22 215:13	331:15
140:14 166:8	387:9 390:24	370:4 373:16	232:5 260:19	<b>triggered</b> 40:4
175:1 177:22	391:20	378:16 379:4	303:17	42:17 313:21
180:3 196:14	<b>touched</b> 58:10	402:6	<b>trained</b> 58:3	336:21
230:16 233:5	176:15	<b>toxicologists</b>	<b>training</b> 45:19	<b>trouble</b> 125:15
234:1,5,9	<b>tough</b> 86:20	46:23 47:4,8	47:17,21 48:17	375:14
254:7 258:2	<b>tox-</b> 45:21	47:16 48:8	49:13 51:17	<b>true</b> 56:15
263:20 264:15	<b>toxic</b> 12:20,22	58:19 387:23	53:2,7 81:18	120:19 125:11
276:18 293:14	344:3,4 396:5	408:3 409:22	129:20 131:5	182:3 226:15
294:2 304:7,20	396:15,16	410:15	132:10 138:14	314:9 335:14
331:1,11,22	<b>toxicity</b> 305:13	<b>toxicology</b> 5:7	267:23 270:4,5	338:10 358:21
333:22 336:16	305:15,16	5:13 7:8 17:10	270:17,24	363:18,20
339:15 343:18	317:24 318:13	17:12,19 18:18	294:24 295:15	365:20 374:6
347:13 348:12	321:4 322:13	19:1,7,17	296:1,20	385:10 387:12
352:20 361:4	325:19 326:1,3	20:20,22 21:2	297:21 299:3	399:4 407:3,17
365:3 372:7	327:8 328:22	22:9 23:13,22	379:6	409:8 411:20
379:13 403:12	329:1 330:6	23:24 24:5,10	<b>transcript</b> 432:7	<b>truth</b> 223:9
420:4	383:3 387:10	24:17,23 25:5	433:17,18	224:2 432:5,5
<b>Today's</b> 8:6	388:24 389:5	25:22 26:1,3	<b>transcription</b>	432:5
<b>told</b> 35:5 52:21	389:14 390:4,7	26:19 46:1	435:5	<b>try</b> 39:19 118:6
116:12,18	395:12,16,22	48:18,21 49:14	<b>translate</b> 281:8	118:17 132:7
156:1 174:4	397:4 408:12	49:16 53:8	<b>transloading</b>	146:8,18 147:5
187:19 193:6	408:24	81:19 82:3	14:11	195:2 208:7
202:6 229:20	<b>toxicokinetics</b>	92:5 129:24	<b>translocate</b>	217:3 258:14
286:19 298:9	406:24	132:11,14	322:16	322:24
331:21,24	<b>toxicological</b>	138:18,21	<b>transmission</b>	<b>trying</b> 54:24
334:10 367:15	14:10 21:1,8	222:17 270:5	6:11 217:15	65:5 70:21
<b>tools</b> 396:10	21:11,16 22:2	271:1 281:21	327:22	71:16 91:10
<b>top</b> 73:12 75:5,5	41:9,10 49:17	296:22 312:2	<b>transport</b> 142:9	98:11 131:21
75:9 80:12	133:22 262:11	330:10 343:19	142:17 144:2	141:15 155:4
97:7 143:22	262:15,18	343:22 387:13	147:2 149:22	166:3 192:24
144:14 198:12	271:4 387:20	387:16,20	150:2,16	195:5 269:15
204:3 220:3	388:6	388:9 394:16	170:23 171:1,7	274:1 295:1
223:19 250:21	<b>toxicologist</b>	398:17 404:24	185:4 206:14	297:5 299:12
262:9 289:17	13:12 21:5,24	407:9,19 408:9	215:12 425:7	334:7 337:2
341:15,22	27:6 34:4 39:5	409:14,15	<b>transported</b>	341:12 360:9
429:22	41:8 44:14	<b>tract</b> 89:24 91:7	424:1	392:11 420:8
<b>topic</b> 64:12	45:16,19,22	108:15 109:6	<b>traveled</b> 182:18	429:20
65:15 112:20	51:17 53:1	110:11,20	190:1	<b>tubes</b> 158:24
121:1,14 127:7	56:2 57:5,20	111:5,10,18,24	<b>treat</b> 22:10 46:3	175:9 176:3
180:4 186:3	58:3 59:22,24	116:9 120:12	<b>tree</b> 239:11,11	182:19 183:7
203:13 234:8	60:15 91:17	135:22 137:14	<b>trial</b> 341:8	184:14 190:1
<b>topics</b> 21:11	97:24 98:18	148:15,23	<b>trick</b> 197:15	228:9 326:16
52:19 64:10	99:12,16 122:6	149:11 152:1,6	<b>tried</b> 285:9	<b>TUCKER</b> 2:18
185:23 203:16	129:23 131:8	152:18 168:10	290:22 292:8	3:7

<b>tumor</b> 161:2,16 162:20	220:5,7,14 223:15 224:16	<b>Tuttle-20</b> 6:8 197:6	72:11 <b>Tuttle-8</b> 5:12	<b>underlying</b> 152:18
<b>tumors</b> 161:4 162:18 263:8 264:13 272:14 274:10 276:12	235:8 249:9 250:19 252:8 256:7 261:20 272:10 273:10	<b>Tuttle-21</b> 6:10 201:17	82:2 <b>Tuttle-9</b> 5:14	<b>understand</b> 9:16 15:11 22:10
<b>turn</b> 18:14 82:11 107:10 108:10 132:1 135:8 142:4 143:20 158:2 160:10 167:20 181:11 204:1 321:3 399:21	274:6 276:3,20 278:9,13,23 279:24 280:22 284:14,20 293:5 320:21 327:7 328:20 329:2 340:13 343:3 347:23 351:11,22	<b>Tuttle-22</b> 6:11 217:15	<b>two</b> 75:7 93:15 98:20 145:9,19 146:18 152:7 158:20 161:18 176:8 179:13 180:11,12 182:17 184:11 189:22,24 251:19 279:23 315:3 331:22 351:4 363:15 408:10,23 417:5 420:23 422:17	28:9 31:7 46:2 46:11 47:3,5 47:24 52:18 69:12 78:6 90:21 111:20 111:22 113:22 116:18,20 121:2 122:10 125:17 128:8 130:7 134:20 145:8 155:9,11 155:14 162:10 165:23 166:1 177:20 180:2 191:7 192:22 192:24 196:2 204:23 208:21 212:8 213:13 219:19 221:8 241:6 247:16 249:17 291:14 297:5 299:17 319:3 358:23 368:9 391:23 393:22 397:1 404:22 418:17 428:21
<b>turned</b> 44:13 45:6,10,11 201:15 369:9 421:15	352:19 353:13 356:12 357:3 357:15 359:11 362:11,24 369:6,10 398:15 399:22 405:19 415:7 416:2 419:9 432:4 435:4,12	<b>Tuttle-23</b> 6:13 224:18	<b>two-page</b> 50:8 293:10	
<b>turning</b> 350:10		<b>Tuttle-24</b> 6:14 249:11	<b>type</b> 16:23 99:20 215:20 228:11 245:1 288:1,10 288:19 326:17 327:2,6	
<b>Tuttle</b> 1:14 4:6 5:1,4,5,9,16 6:18 8:11,17 8:21 9:7,11,22 12:4,9,12,22 13:20 14:13 19:14 22:6 26:7,9,21,24 50:8 72:8,14 72:17 82:8 83:8,17 93:7,7 102:20 104:11 106:24 141:6 142:22 157:18 158:18 159:16 159:23 160:2 162:2 164:5 165:7 166:12 168:6 170:10 172:6,20,23 174:13 175:15 179:21 180:23 182:9,22 183:11 187:14 190:10 194:7 194:21 196:19 197:3 201:22 217:10 219:5,6	<b>Tuttle-1</b> 5:4 9:7 <b>Tuttle-10</b> 5:15 93:12 <b>Tuttle-11</b> 5:16 102:20 <b>Tuttle-12</b> 5:18 141:9 <b>Tuttle-13</b> 5:19 157:20 <b>Tuttle-14</b> 5:20 159:19 <b>Tuttle-15</b> 5:22 164:12 <b>Tuttle-16</b> 6:2 166:15 <b>Tuttle-17</b> 6:4 170:13 <b>Tuttle-18</b> 6:5 172:8 <b>Tuttle-19</b> 6:7 174:16 <b>Tuttle-2</b> 5:5 12:4	<b>Tuttle-25</b> 6:15 261:13 <b>Tuttle-26</b> 6:16 273:12 <b>Tuttle-27</b> 6:17 280:3 <b>Tuttle-28</b> 6:18 284:20 <b>Tuttle-29</b> 6:19 293:7 <b>Tuttle-3</b> 5:6 17:18 <b>Tuttle-30</b> 6:20 320:17 <b>Tuttle-31</b> 6:21 340:15 <b>Tuttle-32</b> 7:2 348:1 <b>Tuttle-33</b> 7:4 351:13 <b>Tuttle-34</b> 7:6 362:13 <b>Tuttle-35</b> 7:7 386:12 <b>Tuttle-36</b> 7:8 398:17 <b>Tuttle-37</b> 7:10 415:9 <b>Tuttle-38</b> 7:12 419:11 <b>Tuttle-4</b> 5:8 20:2 <b>Tuttle-5</b> 5:9 26:9 <b>Tuttle-6</b> 5:10 50:4 <b>Tuttle-7</b> 5:11	<b>types</b> 131:7 <b>typos</b> 98:4,13	
			<hr/> <b>U</b> <hr/>	
			<b>ultimately</b> 33:9 131:13 133:4 135:3 176:4 271:7 285:11 335:22 <b>Ultrastructural</b> 174:22 <b>umbrella</b> 130:6 <b>unable</b> 70:22 <b>unclear</b> 134:13 <b>undergo</b> 148:12 <b>undergone</b> 291:5 <b>undergrad</b> 80:10 <b>underlie</b> 408:11 408:23	<b>understanding</b> 15:15,16,21 24:12 32:12 53:3 89:17 100:22 102:4 111:12 155:18 156:13 167:15 250:2,5,8 290:16 291:6 291:20 330:9 345:2,9 364:21 <b>understood</b> 27:7 35:7 69:18 114:2 131:2 326:6 397:10 <b>undertake</b> 38:20

<b>undertaken</b> 57:5 291:4	131:12 133:23 144:5 145:4	79:4,12,24 115:10 227:3	<b>videographer</b> 3:20 8:3,5 86:8	<b>W</b>
<b>unfair</b> 115:3	157:6 186:13	237:6	86:12 147:14	<b>W-E-H-N-E-R</b>
<b>unfamiliar</b> 264:1	186:16 198:13	<b>vagina</b> 158:22	147:18 240:5,9	251:17
<b>unfold</b> 317:4	199:11 222:6	159:8 165:3,14	280:15 283:24	<b>W.J</b> 159:24
<b>unfortunately</b> 253:22	243:16 244:8	167:5,11,18,19	284:4 351:2	<b>wait</b> 275:12
<b>unidentified</b> 100:22	245:3 249:19	173:6,14	364:7,11	371:22
<b>unintended</b> 12:14	249:21 250:6,6	182:17 183:6	431:19	<b>want</b> 10:13,16
<b>Union</b> 3:10	252:23 254:9	189:22 199:14	<b>videotaped</b> 1:14	22:8 31:7
<b>United</b> 1:1 80:22	257:2 263:7	199:15 213:21	107:4	35:23 50:9
350:19 352:10	264:13 267:23	214:4,9 215:12	<b>view</b> 57:22	52:17 69:20
352:21 353:13	271:15,16	228:5 232:14	84:10 130:16	70:9 84:1 86:4
354:17 359:6	272:13 273:19	<b>vaginal</b> 159:5	130:17 133:10	90:21 123:21
<b>universal</b> 390:6	274:9 275:24	169:13 195:16	149:16	124:19 132:5
395:15	276:11 289:4	213:15 214:16	<b>viewpoint</b> 74:1	133:7 134:1,14
<b>universally</b> 80:21	296:19 297:22	<b>vague</b> 365:4	76:7,9 112:20	135:15 136:4,7
<b>University</b> 384:19 385:2,8	344:13,18,22	<b>vaguely</b> 59:20	114:12 115:18	147:6 148:7
385:16	345:5,15	80:16 81:8	207:16	151:18 156:9
<b>unpublished</b> 105:4,17,24	394:19 411:16	410:23	<b>viewpoints</b>	165:9,23 167:8
106:9	416:4 425:16	<b>validated</b> 269:6	73:19,20,23	181:5,11
<b>unsound</b> 109:23	426:8,16	271:8	74:9 75:14	196:15 200:12
303:8	427:16,17,24	<b>value</b> 420:19	76:4,20 77:5	205:19 217:3
<b>upper</b> 175:8	428:3,8,11,16	422:14	77:17 78:8	220:15 221:11
176:2	429:13 430:1,4	<b>variables</b> 257:5	80:4 82:23	221:21 240:18
<b>upstream</b> 253:9	430:5	<b>variation</b> 418:1	83:4,16,18	241:11 247:15
253:9	<b>useful</b> 256:1	<b>variations</b> 169:8	86:23 87:6	249:23,24
<b>uptake</b> 316:20	301:13 393:12	<b>variety</b> 290:11	114:22 115:5	273:6 277:11
<b>upward</b> 128:6	394:15 396:10	<b>various</b> 17:13	115:13 116:2	277:22 302:8
<b>upwards</b> 124:16	396:24 397:15	57:22 81:15	121:15 203:22	304:7 311:20
135:19	408:2 409:22	152:16 210:3	204:12 207:12	311:20 344:13
<b>use</b> 9:3 27:5,10	410:14	329:24 394:16	227:3 233:12	363:6 364:1,2
27:24 28:13,21	<b>usefully</b> 75:21	419:2	300:4,7,8	397:8 399:3
29:3,4 30:1	76:14	<b>vary</b> 314:20	305:8	402:20 403:3
34:15 35:13	<b>uses</b> 150:5	315:2	<b>Virginia</b> 2:15	409:14 415:19
36:14,17 37:1	272:19 346:20	<b>Venter</b> 5:22	<b>visited</b> 327:1	423:21 427:2
37:7 42:6,24	<b>usually</b> 405:24	164:6,12	<b>Vitae</b> 5:9 26:9	<b>wanted</b> 11:3
43:11 59:6	407:5	<b>verbatim</b> 253:24	<b>vitreous</b> 327:15	28:12 31:16
60:15,21 77:7	<b>uterine</b> 170:22	308:1 353:17	<b>vitro</b> 306:4,15	35:6 74:21
79:4 81:14	171:10,14,23	432:7	307:21 387:17	116:24 162:24
98:14 110:1	281:10	<b>verify</b> 166:4	387:23 388:4	165:19 179:18
	<b>uterotubal</b> 170:23	<b>versed</b> 22:19	393:12 394:15	241:14 363:14
	<b>V</b>	291:10,16	410:13	<b>wanting</b> 52:12
	<b>v</b> 13:1,2,3,5,6,7	297:13	<b>vivo</b> 306:4,15	398:6
	13:8 14:6,16	<b>versus</b> 206:3	307:21 387:23	<b>warning</b> 51:1
	<b>vacuum</b> 78:11	245:23 311:13	388:5 393:5	54:6,7,11 55:4
		<b>veterinary</b> 383:16,18	394:3,14	55:24 429:16
			<b>Volume</b> 184:24	430:8,13,17



<b>warnings</b> 54:17 54:21 55:7 56:18	245:2,11 246:17,18 248:21 260:15	6:17,19 249:4 249:11,15 250:18,23	362:21 363:18 370:4 376:4 379:24 380:10	308:19,19 309:4,6,7,8,9 318:20 353:20
<b>washing</b> 289:23	261:4 274:18	251:2,9,19	386:9 432:10	354:5 359:5
<b>Washington</b> 3:14	280:6 281:15 284:4 296:4	252:12 254:11 254:20 256:6	432:11 433:1	387:2
<b>wasn't</b> 40:6,19 40:20 41:19 43:14,15 182:24 384:13	300:1 316:9 318:23 323:16 325:21 327:12 329:17 330:7 331:9 339:15 339:17 355:5 362:18 364:11	259:6,9 260:3 261:13 262:10 278:20 279:4 280:3 282:6 293:3,7,15 294:1 344:16 344:17	<b>witness'</b> 212:10 365:18 379:12	<b>work</b> 15:24 16:16 21:4,24 27:6 29:5 31:8 32:17,24 33:11 33:16 38:11 53:8,18 55:12 57:5 61:22 85:3 95:1 99:21 100:7,12 120:3 131:7,11 133:4 168:1 215:19 216:4 241:12 262:3 265:10 275:6 276:16 288:14 288:18,23 289:10,10 296:21 302:2 304:4 311:24 312:4 320:6 344:21 372:10 383:21,24
<b>waste</b> 421:1 422:5,20	331:9 339:15 339:17 355:5 362:18 364:11	293:3,7,15 294:1 344:16 344:17	142:10,18 144:3,4,10 147:3 148:12 148:21 149:4,9 149:24 185:5 209:17 210:15 215:6 228:12 240:17 326:19	57:5 61:22 85:3 95:1 99:21 100:7,12 120:3 131:7,11 133:4 168:1 215:19 216:4 241:12 262:3 265:10 275:6 276:16 288:14 288:18,23 289:10,10 296:21 302:2 304:4 311:24 312:4 320:6 344:21 372:10 383:21,24
<b>Watch</b> 284:17	373:16 388:20 424:3 425:17 427:4 430:22 431:20	<b>weigh</b> 40:14 117:21 119:1 120:6,15	148:21 149:4,9 149:24 185:5 209:17 210:15 215:6 228:12 240:17 326:19	85:3 95:1 99:21 100:7,12 120:3 131:7,11 133:4 168:1 215:19 216:4 241:12 262:3 265:10 275:6 276:16 288:14 288:18,23 289:10,10 296:21 302:2 304:4 311:24 312:4 320:6 344:21 372:10 383:21,24
<b>water</b> 126:12,13 126:24 131:16	373:16 388:20 424:3 425:17 427:4 430:22 431:20	<b>weighing</b> 119:13 119:20	148:21 149:4,9 149:24 185:5 209:17 210:15 215:6 228:12 240:17 326:19	85:3 95:1 99:21 100:7,12 120:3 131:7,11 133:4 168:1 215:19 216:4 241:12 262:3 265:10 275:6 276:16 288:14 288:18,23 289:10,10 296:21 302:2 304:4 311:24 312:4 320:6 344:21 372:10 383:21,24
<b>Watson</b> 223:6 223:23	373:16 388:20 424:3 425:17 427:4 430:22 431:20	<b>weight</b> 119:17 200:7 208:1 301:8	<b>wonder</b> 221:10 <b>wondering</b> 246:7 289:1 <b>WOODS</b> 3:12 380:9	85:3 95:1 99:21 100:7,12 120:3 131:7,11 133:4 168:1 215:19 216:4 241:12 262:3 265:10 275:6 276:16 288:14 288:18,23 289:10,10 296:21 302:2 304:4 311:24 312:4 320:6 344:21 372:10 383:21,24
<b>way</b> 22:9 46:2 61:3 71:11 96:12 101:6 181:1 206:23 226:14 254:10 294:6 295:2 334:8 337:3 342:6 351:18 375:24 378:17 386:6 412:18 428:15	<b>we've</b> 48:20 168:5 169:3 172:15 176:12 178:1,8 180:13 185:21 187:14 187:16 188:6 195:15 203:9 207:4,6,12 228:20 232:19 233:3 234:9 242:15 243:3 243:18,22 260:1,1,3 265:20 280:15 304:6 327:1 328:7 340:19 364:14 388:20 431:1	<b>well-discussed</b> 294:12 <b>went</b> 38:11 66:3 67:24 70:24 216:1 385:15 387:7 421:14 421:19	<b>word</b> 73:10,13 73:15 76:10,16 123:24 134:19 150:5 156:2 157:2,6,8 161:7 305:16 315:23 321:22 322:17 338:20 362:2 401:20 410:1	85:3 95:1 99:21 100:7,12 120:3 131:7,11 133:4 168:1 215:19 216:4 241:12 262:3 265:10 275:6 276:16 288:14 288:18,23 289:10,10 296:21 302:2 304:4 311:24 312:4 320:6 344:21 372:10 383:21,24
<b>we'll</b> 69:13 85:24 86:7 92:19 147:12 169:23 206:22 363:23 364:4	<b>we've</b> 48:20 168:5 169:3 172:15 176:12 178:1,8 180:13 185:21 187:14 187:16 188:6 195:15 203:9 207:4,6,12 228:20 232:19 233:3 234:9 242:15 243:3 243:18,22 260:1,1,3 265:20 280:15 304:6 327:1 328:7 340:19 364:14 388:20 431:1	<b>weren't</b> 177:18 191:9,9	<b>wording</b> 83:22 114:16 146:1	85:3 95:1 99:21 100:7,12 120:3 131:7,11 133:4 168:1 215:19 216:4 241:12 262:3 265:10 275:6 276:16 288:14 288:18,23 289:10,10 296:21 302:2 304:4 311:24 312:4 320:6 344:21 372:10 383:21,24
<b>we're</b> 8:3 15:9 21:18,20 30:20 65:5 83:7 86:12 95:12 103:14 119:3 122:22 138:5 146:15 147:18 152:10 155:10 155:14,18 156:17 166:23 177:1 180:5 195:19 204:6 214:15 230:20 240:9 244:7	<b>weak</b> 142:10,18 147:3 149:24 185:5 257:3 279:14 282:11 <b>weaknesses</b> 294:12 <b>website</b> 198:24 199:18,23 200:14 347:10 386:6 <b>week</b> 69:9 71:19 <b>Wehner</b> 6:14,15	<b>what's</b> 400:23 <b>wide</b> 21:10,11 49:15 138:18 290:11 <b>William</b> 341:24 341:24 <b>Wilson</b> 13:2 14:6 <b>witness</b> 8:16 86:1 209:4 224:20 229:19 250:3 254:5 273:21 280:5 280:11,17 331:4 341:6 350:23 351:6 361:14 362:15	<b>words</b> 28:9 57:16,19 77:10 110:1 135:10 136:8,15 142:16 152:7 163:21 185:1 186:13,16 204:3 243:16 243:20 244:6 249:18 254:9 258:1 275:12 289:3 290:5 291:4 308:8,9	85:3 95:1 99:21 100:7,12 120:3 131:7,11 133:4 168:1 215:19 216:4 241:12 262:3 265:10 275:6 276:16 288:14 288:18,23 289:10,10 296:21 302:2 304:4 311:24 312:4 320:6 344:21 372:10 383:21,24
				<b>worked</b> 53:24 54:7,14,20 95:17,24 96:14 97:8 99:23 101:4 102:1 312:11 379:7 <b>workers</b> 13:20 375:23 <b>working</b> 37:21 53:7 95:10,15 147:1 185:3 283:7 <b>workshop</b> 263:5 263:18 279:6 282:10 <b>World</b> 364:23 <b>Worth</b> 1:15,16 8:9 18:12 <b>wouldn't</b> 62:9 62:23 63:1

65:16 139:7	220:24 221:12	142:4 185:14	<b>19</b> 174:14	<b>2/17/77</b> 6:21
214:6 222:18	222:14 293:12	186:4 187:4,10	175:15 179:21	340:15
249:24 334:10	327:23	<b>11:34</b> 147:15,16	202:21,23	<b>2:07</b> 240:8,10
403:3	<b>Zelikoff</b> 108:12	<b>1100</b> 3:8	203:13	<b>2:49</b> 284:1,2
<b>write</b> 304:4	109:4 110:3	<b>1181</b> 252:22	<b>1961</b> 160:1	<b>20</b> 5:8 93:1
309:6 328:20	303:7,20	<b>1182</b> 257:13	182:5,9,16	197:4 202:21
328:24	<b>Zelikoff's</b>	<b>11th</b> 8:6	183:10,16,22	203:15 435:16
<b>writing</b> 98:11	108:22 109:12	<b>12</b> 5:5 104:10,14	184:6	<b>20%</b> 411:4
<b>writings</b> 157:3,7	<b>ZELLERS</b> 2:19	141:7 142:23	<b>1965</b> 5:11 72:11	<b>20004-1454</b> 3:14
<b>written</b> 253:24	399:23	175:5,14	72:18 82:24	<b>2004</b> 6:4,5,11
273:23 274:7	<b>zero</b> 420:22	180:23 432:23	114:23 203:7	84:9 170:13
274:12,19	422:16	<b>12.2</b> 108:11	<b>197</b> 6:8	172:8,12
275:1,15 276:2		109:3	<b>1971</b> 5:20	173:23 217:15
278:6 308:13	<b>0</b>	<b>12:22</b> 147:17	159:19,24	218:3 219:16
308:22 319:22	<b>0.05</b> 420:20	<b>12:24</b> 147:19	160:3 190:6,9	219:23 294:1
<b>wrong</b> 94:11	422:15	<b>13</b> 157:18	190:12 191:12	<b>201</b> 6:10
193:10	<b>07932</b> 3:4	158:19 160:2	193:5	<b>2010</b> 141:20
<b>wrote</b> 278:13	<b>1</b>	182:9,22	<b>1977</b> 342:6	143:1,7
309:7,10		183:11 411:3	<b>1979</b> 5:22 164:6	<b>2012</b> 363:8
329:16 386:20	<b>1</b> 9:12 10:16,23	<b>14</b> 159:17,23	164:12	<b>2014</b> 6:20 225:4
	69:15 82:15	160:2 162:2	<b>1986</b> 6:2 166:15	235:6 320:17
<b>X</b>	172:23 225:4	190:10 194:8	167:21 168:4	327:4 329:17
	355:22	194:21 196:19	<b>1987</b> 394:24	416:15 417:2
<b>Y</b>	<b>1%</b> 355:6	294:10	<b>1988</b> 389:22	417:12,13
<b>Y'all</b> 99:5	356:22 359:20	<b>141</b> 5:18	390:9	<b>2015</b> 388:13
<b>yeah</b> 55:2 95:22	359:21 362:6	<b>14178</b> 249:15	<b>1994</b> 6:14	389:19
262:5 280:17	<b>1.4</b> 301:4	<b>14189</b> 249:15	249:11,15	<b>2016</b> 7:10 415:9
314:22 320:5	<b>1.5</b> 301:4	<b>15</b> 164:5	250:23 252:7	<b>2017</b> 350:19
323:14 356:7	<b>1.6</b> 299:4,20	<b>153</b> 158:17,18	282:8	352:11,21
384:12 421:21	301:4	<b>157</b> 5:19	<b>1996b</b> 206:13	359:6
425:21 431:17	<b>1:56</b> 240:6,7	<b>159</b> 5:20	<b>1997</b> 263:1	<b>2018</b> 33:3,8
<b>year</b> 32:20 40:1	<b>10</b> 93:7,21 94:11	<b>16</b> 165:7 166:13	282:1	203:1 207:3
83:13 178:20	94:16 101:7	167:21 168:6	<b>1999</b> 316:15	<b>2019</b> 1:12 5:2
182:14 294:4	223:19 263:3	176:13		6:7 8:2,7
<b>years</b> 5:5 12:4	351:3	<b>16-2738</b> 1:5	<b>2</b>	174:16,20
35:15 37:16	<b>10/7/04</b> 6:19	<b>164</b> 5:22	<b>2</b> 4:2 12:9,12,22	432:23
42:19 322:23	293:7	<b>166</b> 6:2	13:20 14:2,13	<b>202</b> 3:14
329:16 385:17	<b>10:24</b> 86:9,10	<b>16th</b> 262:24	22:6 68:17	<b>21</b> 5:10 50:4,14
<b>yesterday</b> 93:3	<b>10:34</b> 86:11,13	<b>17</b> 5:6 170:11	70:10 282:3	201:22 202:22
	<b>100C</b> 363:8,11	263:1 282:1,8	321:3 392:5	204:1,3 206:7
<b>Z</b>	<b>102</b> 5:16	342:6 383:4	409:13,15	207:16 212:3
<b>Z-A-R-E-N-S-...</b>	<b>11</b> 1:12 5:2 8:2	<b>170</b> 6:4	<b>2.0</b> 294:13,23	346:22
327:24	75:4,9 102:18	<b>172</b> 6:5	295:1,5,6,10	<b>213</b> 2:21
<b>Z-A-Z-E-N-S-...</b>	104:11,15,18	<b>174</b> 6:7	295:13,18,24	<b>216</b> 3:9
219:8 293:12	106:24 176:11	<b>18</b> 172:6,20,23	296:8 298:8,17	<b>217</b> 6:11
<b>Zaren-</b> 327:23	<b>11.5</b> 107:12,24	219:6,6 220:5	299:1,1 301:14	<b>218</b> 2:9
<b>Zazenski</b> 219:8	108:4 124:13	383:4	301:14	<b>22</b> 217:10 220:8

220:14 327:21 329:7 <b>22311</b> 2:15 <b>224</b> 6:13 <b>23</b> 224:16 225:2 235:8 326:8 <b>24</b> 249:9 250:19 252:8 256:7 <b>249</b> 6:14 <b>25</b> 93:1 261:9,20 272:10 278:10 278:23 415:23 416:13 <b>250</b> 275:9 <b>255</b> 276:14 379:4 <b>26</b> 5:9 82:12 273:10 274:6 276:3,20 278:14 <b>261</b> 6:15 <b>268</b> 160:10,24 161:24 163:7 <b>269-2343</b> 2:10 <b>27</b> 280:1,9,22 306:21 334:23 338:13 <b>271</b> 161:8 163:8 <b>273</b> 6:16 <b>28</b> 158:23 235:4 284:15 <b>280</b> 6:17 <b>284</b> 6:18 <b>29</b> 293:5 301:19 419:1 <b>293</b> 6:19 <b>294</b> 369:9 <b>299</b> 75:5	261:13 <b>3:35</b> 284:3,5 <b>30</b> 86:24 87:5,21 114:17 116:3 182:19 257:20 320:22 327:7 328:21 329:2 329:12 432:10 433:16 <b>300</b> 275:10 <b>305</b> 101:16 102:2,6 <b>31</b> 340:13 341:5 <b>316304</b> 94:13 <b>32</b> 347:23,23 348:21 <b>320</b> 6:20 <b>33</b> 351:11,23 352:19 353:13 356:12 357:3 357:15 359:12 <b>334</b> 2:10 <b>337</b> 2:5 <b>34</b> 158:23 350:10 351:24 352:22 357:14 362:11,24 369:6,10 <b>340</b> 6:21 <b>348</b> 7:2 <b>35</b> 386:9,10 <b>351</b> 7:4 <b>36</b> 398:15 399:22 <b>36103-4160</b> 2:10 <b>362</b> 7:6 <b>37</b> 415:7 416:2 <b>38</b> 280:16,17 419:9 <b>386</b> 7:7 <b>39</b> 389:22 395:1 <b>391</b> 181:10 <b>392</b> 181:11,22 182:3 187:23 190:5 <b>398</b> 7:8	<b>4</b> <b>4</b> 20:6 22:7 26:21 71:23 72:1 83:19 101:14,15 350:13 <b>4/1/14</b> 6:13 224:18 <b>4:56</b> 364:8,9 <b>411</b> 143:20 146:12,24 148:1,3 181:19 185:1 187:16 187:20 <b>415</b> 7:10 <b>419</b> 7:12 <b>42nd</b> 2:20 <b>43</b> 388:14 <b>430-3400</b> 2:21 <b>432</b> 4:9 <b>434</b> 4:10 <b>435</b> 4:11 <b>436</b> 4:12 <b>44113-7213</b> 3:9 <b>45</b> 289:13,18 290:7 <b>463-2400</b> 3:14 <b>4900</b> 2:14	148:6 185:11 185:13 187:3 <b>59</b> 389:23 395:2	<b>6</b> <b>6</b> 50:8 87:8,18 87:19 <b>6:16</b> 431:21,23 <b>60</b> 108:10 <b>60-plus</b> 379:19 <b>600</b> 3:3 <b>63</b> 388:14 <b>636</b> 18:14,17 <b>646</b> 405:16,19 410:9 <b>650</b> 2:15 <b>66</b> 291:1 <b>696-3675</b> 3:9	<b>7</b> <b>7</b> 72:9,15,17 83:8 160:24 223:16 226:10 294:1 326:10 <b>7.1</b> 387:10 <b>7.3.3</b> 201:3 306:22 338:14 <b>7/9/2020</b> 432:22 <b>703</b> 2:16 <b>70801</b> 2:5 <b>709</b> 217:11 <b>71</b> 162:15 194:7 194:19,20 196:19 <b>72</b> 5:11 71:12 158:3 <b>740</b> 5:10 50:4,15 51:8 <b>740.1</b> 50:15,24 <b>77</b> 302:10	<b>8</b> <b>8</b> 4:3,7 81:24 82:8 83:17 <b>800</b> 423:16 <b>802-4352</b> 2:5 <b>815</b> 1:16	<b>82</b> 5:12 <b>87</b> 395:6 <b>877.370.3377</b> 1:23 <b>88</b> 14:6	<b>9</b> <b>9</b> 5:4 93:7,20 94:8,10,12 101:7,13 <b>9/17/97</b> 6:17 280:3 <b>9:08</b> 1:17 8:2,7 <b>90071</b> 2:21 <b>917.591.5672</b> 1:23 <b>93</b> 5:14,15,18 141:10 142:22 143:11 144:22 145:20 180:24 184:24 187:16 190:6 <b>931-5500</b> 2:16 <b>950</b> 3:8 <b>973</b> 3:4 <b>975</b> 3:13
<b>3</b> <b>3</b> 17:23 19:14 101:14 160:23 199:6 405:13 405:19 410:10 <b>3.0</b> 68:18,21 69:22 70:10 <b>3/17/97</b> 6:15	<b>3</b> <b>3</b> 17:23 19:14 101:14 160:23 199:6 405:13 405:19 410:10 <b>3.0</b> 68:18,21 69:22 70:10 <b>3/17/97</b> 6:15	<b>5</b> <b>5</b> 26:7 71:24 72:1 73:17 83:19 87:15 204:10 226:9 326:9 369:10 <b>5:06</b> 364:10,12 <b>50</b> 5:10 <b>501</b> 2:4 <b>515</b> 2:20 <b>54</b> 399:21 400:2 400:3 401:12 412:20 <b>549-7000</b> 3:4 <b>57</b> 107:11 123:23 124:10 124:13 125:20 135:8 142:2						

# Exhibit R

# *Casarett and Doull's* **TOXICOLOGY**

## **The Basic Science of Poisons**

**Eighth Edition**

editor

**Curtis D. Klaassen, PhD**

University Distinguished Professor  
Division of Gastroenterology  
Department of Internal Medicine  
College of Medicine  
University of Kansas  
Kansas City, Kansas



**Medical**

New York Chicago San Francisco Lisbon London Madrid Mexico City  
Milan New Delhi San Juan Seoul Singapore Sydney Toronto



# chapter

## Principles of Toxicology

David L. Eaton and Steven G. Gilbert

### Introduction to Toxicology

Different Areas of Toxicology  
Toxicology and Society  
General Characteristics  
of the Toxic Response

### Classification of Toxic Agents

### Spectrum of Undesired Effects

Allergic Reactions  
Idiosyncratic Reactions  
Immediate versus Delayed Toxicity  
Reversible versus Irreversible  
Toxic Effects  
Local versus Systemic Toxicity  
Interaction of Chemicals  
Tolerance

### Characteristics of Exposure

Route and Site of Exposure  
Duration and Frequency of Exposure

### Dose-Response Relationship

Individual, or Graded,  
Dose-Response Relationships

### Quantal Dose-Response

Relationships  
Shape of the Dose-Response Curve  
*Essential Nutrients*  
*Hormesis*  
*Threshold*  
*Nonmonotonic Dose-Response Curves*  
Assumptions in Deriving the  
Dose-Response Relationship  
Evaluating the Dose-Response  
Relationship  
*Comparison of Dose Responses*  
*Therapeutic Index*  
*Margins of Safety and Exposure*  
*Potency versus Efficacy*

### Variation in Toxic Responses

Selective Toxicity  
Species Differences  
Individual Differences in Response

### Descriptive Animal

**Toxicity Tests**  
Acute Toxicity Testing  
Skin and Eye Irritations

### Sensitization

Subacute (Repeated-Dose Study)  
Subchronic  
Chronic  
Developmental and Reproductive  
Toxicity  
Mutagenicity  
Oncogenicity Bioassays  
Neurotoxicity Assessment  
Immunotoxicity Assessment  
Other Descriptive Toxicity Tests

### Toxicogenomics

Genomics  
Epigenetics/Epigenomics  
Transcriptomics  
Proteomics  
Metabonomics/Metabolomics  
Bioinformatics  
Challenges in Using "Omics"  
Technologies for Predictive  
Toxicology and Risk  
Assessment

## INTRODUCTION TO TOXICOLOGY

*Toxicology* is the study of the adverse effects of chemical or physical agents on living organisms. A *toxicologist* is trained to examine and communicate the nature of those effects on human, animal, and environmental health. Toxicological research examines the cellular, biochemical, and molecular mechanisms of action as well as functional effects such as neurobehavioral and immunological, and assesses the probability of their occurrence. Fundamental to this process is characterizing the relation of exposure (or dose) to the response. *Risk assessment* is the quantitative estimate of the potential effects on human health and environmental significance of various types of chemical exposures (eg, pesticide residues in food, contaminants in drinking water). The variety of potential adverse effects and the diversity of chemicals in the environment make toxicology a broad science, which often demands specialization in one area of toxicology. Our society's dependence on chemicals and the need to assess potential hazards have made toxicologists an increasingly important part of the decision-making processes.

## Different Areas of Toxicology

The professional activities of toxicologists fall into 3 main categories: descriptive, mechanistic, and regulatory (Fig. 2-1). Although each has distinctive characteristics, each contributes to the other, and all are vitally important to chemical risk assessment (see Chap. 4).

A *mechanistic toxicologist* is concerned with identifying and understanding the cellular, biochemical, and molecular mechanisms by which chemicals exert toxic effects on living organisms (see Chap. 3 for a detailed discussion of mechanisms of toxicity). The results of mechanistic studies are very important in many areas of applied toxicology. In risk assessment, mechanistic data may be very useful in demonstrating that an adverse outcome (eg, cancer, birth defects) observed in laboratory animals is directly relevant to humans. For example, the relative toxic potential of organophosphorus (OP) insecticides in humans, rodents, and insects can be accurately predicted on the basis of an understanding of common mechanisms (inhibition of acetylcholinesterase) and differences in biotransformation for these insecticides among the different species. Similarly, mechanistic data may be very useful in identifying



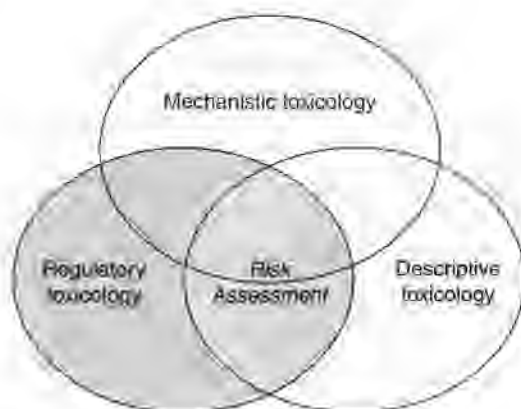


Figure 2-1. Graphical representation of the interconnections between different areas of toxicology.

adverse responses in experimental animals that may not be relevant to humans. For example, the propensity of the widely used artificial sweetener saccharin to cause bladder cancer in rats may not be relevant to humans at normal dietary intake rates. This is because mechanistic studies have demonstrated that bladder cancer is induced only under conditions where saccharin is at such a high concentration in the urine that it forms a crystalline precipitate (Cohen, 1998). Dose-response studies suggest that such high concentrations would not be achieved in the human bladder even after extensive dietary consumption.

Mechanistic data are also useful in the design and production of safer alternative chemicals and in rational therapy for chemical poisoning and treatment of disease. For example, the drug thalidomide was originally marketed in Europe and Australia as a sedative agent for pregnant women. However, it was banned for clinical use in 1962 because of devastating birth defects that occurred if the drug was ingested during a critical period in pregnancy. But mechanistic studies over the past several decades have demonstrated that this drug may have a unique molecular mechanism of action that interferes with the expression of certain genes responsible for blood vessel formation (angiogenesis). With an understanding of this mechanism, thalidomide has been "rediscovered" as a valuable therapeutic agent that may be highly effective in the treatment of certain infectious diseases (eg, leprosy) and multiple myeloma. This provides an interesting example of how a highly toxic drug with selectivity toward a specific population (pregnant women) can be used relatively safely with proper precautions. Following its approval for therapeutic use in 1998, a program was established that required all clinicians, pharmacists, and patients who receive thalidomide to enroll in a specific program (System for Thalidomide Education and Prescribing Safety [STEPS]). The population at risk for the potential teratogenic effects of thalidomide (all women of childbearing age) was required to use 2 forms of birth control, and also have a negative pregnancy test within 24 hours of beginning therapy, and periodically thereafter. Among the patients registered with the STEPS program, 6000 were females of childbearing age. Remarkably, after 6 years of use, only 1 patient actually received thalidomide during her pregnancy. She initially tested negative at the beginning of therapy; on a subsequent test she was identified as positive, and the drug was stopped. The pregnancy ended up as a miscarriage (Uhl *et al.*, 2006). Thus, a clear understanding of mechanism of action led to the development of strict prescribing guidelines and patient monitoring, thereby allowing a potentially dangerous drug to be used safely and effectively to treat disease in tens of thousands of patients who would otherwise not have benefited from the therapeutic actions of the drug (Lary *et al.*, 1999).

In addition to aiding directly in the identification, treatment, and prevention of chemical toxicity, an understanding of the mechanisms of toxic action contributes to the knowledge of basic physiology, pharmacology, cell biology, and biochemistry. The advent of new technologies in molecular biology and genomics now provides mechanistic toxicologists with the tools to explore exactly how humans may differ from laboratory animals in their response to toxic substances. These same tools are also being utilized to identify individuals who are genetically susceptible to factors in the environment or respond differently to a chemical exposure. For example, a small percentage of the population genetically lacks the ability to detoxify the chemotherapeutic drug, 6-mercaptopurine, used in the treatment of some forms of leukemia. Young children with leukemia who are homozygous for this genetic trait (about 1 in 300) may experience serious toxic effects from a standard therapeutic dose of this drug (Weinshilboum *et al.*, 1999). Numerous genetic tests for polymorphisms in drug-metabolizing enzymes and transporters are now available that can identify genetically susceptible individuals in advance of pharmacological treatment (Eichelbaum *et al.*, 2006).

The development of new approaches in identifying associations between diseases or adverse outcomes and common genetic variants (polymorphisms) has changed from a focus on individual candidate genes to "genome-wide association studies" (GWAS). GWAS are based on a rapid scan of hundreds of thousands of specific genetic variants (markers called "tag SNP") across the genome of persons affected by a particular disorder or adverse-response phenotype and persons who are not affected, with robust statistical tests to identify associations between a specific genetic marker and the phenotype (eg, disease state or adverse drug response). These tools have resulted in the discovery of many "gene-environment interactions," including associations between adverse drug responses and particular genetic polymorphisms (Wang *et al.*, 2011). Moving from the single, "candidate gene" approach to genome-wide studies has led to the development of the relatively new fields of pharmacogenomics and toxicogenomics. These areas provide an exciting opportunity for mechanistic toxicologists to identify and protect genetically susceptible individuals from harmful environmental exposures, and to customize drug therapies that enhance efficacy and minimize toxicity, based on an individual's genetic makeup.

A *descriptive toxicologist* is concerned directly with toxicity testing, which provides information for safety evaluation and regulatory requirements. The appropriate toxicity tests (as described later in this chapter and other chapters) in cell culture systems or experimental animals are designed to yield information to evaluate risks posed to humans and the environment from exposure to specific chemicals. The concern may be limited to effects on humans, as in the case of drugs and food additives. Toxicologists in the chemical industry, however, must be concerned not only with the risk posed by a company's chemicals (insecticides, herbicides, solvents, etc) to humans but also with potential effects on fish, birds, and plants, as well as other factors that might disturb the balance of the ecosystem. Descriptive toxicology is of course not divorced from mechanistic studies, as such studies provide important clues to a chemical's mechanism of action, and thus contribute to the development of mechanistic toxicology through hypothesis generation. Such studies are also a key component of risk assessments that are used by regulatory toxicologists. The development of so-called omics technologies (genomics, transcriptomics, proteomics, metabolomics/metabonomics, etc) forms the basis of the subdiscipline of toxicogenomics. The application of these technologies to toxicity testing is in many ways "descriptive" in nature, yet affords great mechanistic insights into how chemicals produce their toxic effects. This exciting area of toxicology is discussed in more detail later in the chapter.



A *regulatory toxicologist* has the responsibility for deciding, on the basis of data provided by descriptive and mechanistic toxicologists, whether a drug or other chemical poses a sufficiently low risk (or, in the case of drugs, a favorable risk/benefit profile) to be marketed for a stated purpose or subsequent human or environmental exposure resulting from its use. The Food and Drug Administration (FDA) is responsible for allowing drugs, cosmetics, and food additives to be sold in the market according to the Federal Food, Drug and Cosmetic Act (FFDCA). The US Environmental Protection Agency (EPA) is responsible for regulating most other chemicals according to a variety of different legislative acts, including the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA), the Toxic Substances Control Act (TSCA), the Resource Conservation and Recovery Act (RCRA), the Safe Drinking Water Act, and the Clean Air Act. In 1996, the US Congress passed the Food Quality Protection Act (FQPA) that fundamentally changed the pesticide and food safety laws to consider stricter safety standards particularly for infants and children, who were recognized as more susceptible to health effects of pesticides. The EPA is also responsible for enforcing the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA), later revised as the Superfund Amendments Reauthorization Act (SARA), more commonly called the Superfund Act. This regulation provides direction and financial support for the cleanup of waste sites that contain toxic chemicals that may present a risk to human health or the environment. The Occupational Safety and Health Administration (OSHA) of the Department of Labor was established to ensure that safe and healthful conditions exist in the workplace. The National Institute for Occupational Safety and Health (NIOSH) as part of the Centers for Disease Control and Prevention (CDC) in the Department of Health and Human Services (DHHS) is responsible for conducting research and making recommendations for the prevention of work-related injury and illness. The Consumer Product Safety Commission (CPSC) is responsible for protecting consumers from hazardous household substances, whereas the Department of Transportation (DOT) ensures that materials shipped in interstate commerce are labeled and packaged in a manner consistent with the degree of hazard they present. The Nuclear Regulatory Commission (NRC), established in 1974, regulates the civilian use of nuclear material to protect public health and safety, and the environment. Regulatory toxicologists are also involved in the establishment of standards for the amount of chemicals permitted in ambient air, industrial atmospheres, and drinking water, often integrating scientific information from basic descriptive and mechanistic toxicology studies with the principles and approaches used for risk assessment (see Chap. 4).

In addition to the above categories, there are other specialized areas of toxicology such as forensic, clinical, and environmental toxicology. *Forensic toxicology* is a hybrid of analytic chemistry and fundamental toxicological principles. It is concerned primarily with the medicolegal aspects of the harmful effects of chemicals on humans and animals. The expertise of forensic toxicologists is involved primarily to aid in establishing the cause of death and determining its circumstances in a post-mortem investigation (see Chap. 31). *Clinical toxicology* designates an area of professional emphasis in the realm of medical science that is concerned with disease caused by or uniquely associated with toxic substances (see Chap. 32). Generally, clinical toxicologists are physicians who receive specialized training in emergency medicine and poison management. Efforts are directed at treating patients poisoned with drugs or other chemicals and at the development of new techniques to treat those intoxications. Public information about treatment and prevention is often provided through the national network of poison

control centers. *Environmental toxicology* focuses on the impacts of chemical pollutants in the environment on biological organisms. Although toxicologists concerned with the effects of environmental pollutants on human health fit into this definition, it is most commonly associated with studies on the impacts of chemicals on nonhuman organisms such as fish, birds, terrestrial animals, and plants. *Ecotoxicology* is a specialized area within environmental toxicology that focuses more specifically on the impacts of toxic substances on population dynamics in an ecosystem. The transport, fate, and interactions of chemicals in the environment constitute a critical component of both environmental toxicology and ecotoxicology.

## Toxicology and Society

Information from the toxicological sciences, gained by experience or research, has a growing influence on our personal lives as well as on human and environmental health across the globe. Knowledge about the toxicological effects of a compound affects consumer products, drugs, manufacturing processes, waste cleanup, regulatory action, civil disputes, and broad policy decisions. The expanding influence of toxicology on societal issues is accompanied by the responsibility to be increasingly sensitive to the ethical, legal, and social implications of toxicological research and testing.

The convergence of multiple elements has highlighted the evolving ethical dynamics of toxicology. First, experience and new discoveries in the biological sciences have emphasized our interconnectedness with nature and the need for well-articulated visions of human, animal, and environmental health. One vision is that we have "condition(s) that ensure that all living things have the best opportunity to reach and maintain their full genetic potential" (Gilbert, 2003a). Second, we have experience with the health consequences of exposure to such things as lead, asbestos, and tobacco, along with the detailed mechanistic research to understand the long-term risks to individuals and society. This has precipitated many regulatory and legal actions and public policy decisions, not to mention costly and time-consuming lawsuits. Third, we have an increasingly well-defined framework for discussing our social and ethical responsibilities. There is growing recognition that ethics play a crucial role in public health decision making that involves conflicts between individual, corporate, and social justice goals (Callahan and Jennings, 2002; Kass, 2001; Lee, 2002). Fourth is the appreciation that all research involving humans or animals must be conducted in a responsible and ethical manner. Fifth is managing both the uncertainty and biological variability inherent in the biological sciences. Decision making often includes making judgments with limited or uncertain information, which often includes an overlay of individual values and ethics. Finally, individuals involved in toxicological research must be aware of and accountable to their own individual biases and possible conflicts of interest and adhere to the highest ethical standards of the profession (Maurissen *et al.*, 2005; Coble *et al.*, 2009; Gilbert and Eaton, 2009).

Ethical reasoning and philosophy has a long and deep history, but more pragmatic bioethical reasoning can be traced to Leopold, who is arguably America's first bioethicist: "A thing is right when it tends to preserve the integrity, stability, and beauty of the biotic community. It is wrong when it tends otherwise" (Leopold, 1949). The essence of toxicology is to understand the effects of chemicals on the biotic community. This broader definition of an ethic became more focused with examples such as the mercury poisoning in Minamata Bay, Japan, thalidomide, and the effects of pesticides as brought to public awareness by Carson's *Silent Spring* (Carson, 1962). In the United States, these events supported the public and



political will to establish the EPA and strengthen the FDA and other regulations designed to protect human and environmental health. The knowledge that some segments of our society were differentially at risk from chemical exposures evolved into an appreciation of environmental justice (Corburn, 2002; EPA, 2005; Lee, 2002; Morello-Frosch *et al.*, 2002). The EPA defines environmental justice as “the fair treatment and meaningful involvement of all people regardless of race, color, national origin, or income with respect to the development, implementation, and enforcement of environmental laws, regulations, and policies...” (EPA, 2005). Environmental justice is now an important component of numerous community-based programs of interest, and is relevant to the field of toxicology (Nweke, 2011). There is growing recognition of the direct financial and indirect costs to individuals and society from environmental exposures that are not equally distributed across society (Landrigan *et al.*, 2002).

On a parallel track, biomedical ethics developed out of the lessons of World War II and related abuses of human subjects. The 4 principle of biomedical ethics—respect for autonomy, beneficence (do good), nonmaleficence (do no harm), and justice (be fair)—became well established as a basis for decision making in health care settings (Beauchamp and Childress, 1994). These principles formed the basis of rules and regulations regarding the conduct of human research. The demands of ethics and science made it clear that the highest standards of care produced the best results in both human and animal research. Rules and regulations regarding the housing and conduct of animal studies evolved similarly. Professional toxicology societies now require their members to adhere to the highest ethical standards when conducting research with humans or animals. A further refinement and expansion of biomedical ethical principles is the development of community-based participatory research that takes into consideration community needs to ensure the best results and benefit to the community (Arcury *et al.*, 2001; Gilbert, 2006; O’Fallon and Dearry, 2002).

A glance at the daily newspaper confirms the number of current, sometimes controversial issues that are relevant to the field of toxicology. Decisions and action are often demanded or required even when there is a certain level of uncertainty in the toxicological data. The classic example of this challenge is establishing causation of the health effects of tobacco products. In part to address issues related to the health effects of tobacco products, Hill, a distinguished epidemiologist, defined a set of guidelines for evaluating “causation”—for example, whether a causal connection between a particular “exposure” and a particular outcome, condition, or disease can be scientifically established (Hill, 1965). These criteria are briefly summarized as follows:

1. Strength of association (relationship between independent and dependent variables)
2. Consistency of findings (replication of results by different studies)
3. Biological gradient (strength of the dose-response relationship)
4. Temporal sequence (“cause” before effect)
5. Biological or theoretical plausibility (mechanism of action)
6. Coherence with established knowledge (no competing hypotheses)
7. Specificity of association (cause is tightly linked to an outcome)

Although the guidelines provided by Hill were originally designed for interpretation of epidemiological data, they are equally applicable to establishing causation in toxicology, which often relies on a mix of both epidemiological and toxicological data.

Quantitative risk assessment was developed in part to address issues of uncertainty related to potential harm. The risk assessment process summarizes data for risk managers and other decision makers, who must take into consideration to some degree the qualitative elements of ethical, social, and political issues. Whereas risk management clearly has an ethical and values-based aspect, risk assessment is not immune from the influence of one’s values, bias, or perspective. Ultimately action is required and as Hill (1965) noted: “All scientific work is incomplete—whether it be observational or experimental. All scientific work is liable to be upset or modified by advancing knowledge. That does not confer upon us a freedom to ignore the knowledge we already have or postpone the action that it appears to demand at a given time.” These so-called Bradford Hill criteria were developed largely as a “weight-of-evidence” approach for interpreting a body of epidemiology data, yet are relevant as well to toxicology. Guzelian *et al.* (2005) provided a more detailed, evidence-based approach for determining causation in toxicology, primarily for application in the legal arena.

Although the scientific data may be the same, there are substantial differences in how toxicological data are used in a regulatory framework to protect public health versus establishing individual causation in the courtroom (Eaton, 2003). The approach to regulatory decision making is in part directed by policy. For example, the experience with thalidomide and other drugs motivated the US Congress to give the FDA broad power to ensure the efficacy and safety of new medicines or medical procedures. In this situation the pharmaceutical company or proponents of an activity must invest in the appropriate animal and human studies to demonstrate safety of the product. In general, a relatively precautionary approach has historically been taken with regard to drugs and medical devices. The approach to industrial chemicals is defined by the Toxic Substance Control Act and does not stipulate such a rigorous approach when introducing a new chemical into commerce.

Building on the work of Hill and others particularly from Europe, the Precautionary Principle was defined at the Wingspread Conference, in 1998: “When an activity raises threats of harm to human health or the environment, precautionary measures should be taken even if some cause and effect relationships are not fully established scientifically” (Gilbert, 2005b; Myers and Raffensperger, 2006; Raffensperger and Tickner, 1999). The precautionary principle incorporates elements of science and ethical philosophy into a single statement, acknowledging that ethics and values are part of the decision-making process. Although the conceptual value of the precautionary principle to public health protection is obvious, its actual implementation in toxicological risk assessment is not straightforward, and remains a point of considerable debate (Marchant, 2003; Goldstein, 2006; Peterson, 2006). The challenge remains to develop a regulatory environment that is responsive to issues of public health and the stewardship of societal resources (Simon, 2011).

With the increased relevance of toxicological data and evaluation in issues fundamental to society, there has been increased awareness of the possibility of conflicts of interest influencing the decision-making process (Maurissen *et al.*, 2005). The disclosure of conflicts of interest as well as the development of appropriate guidelines continues to be a challenge (NAS, 2003; Gozner, 2004; Krinsky and Rothenberg, 2001). These issues go to the core of one’s individual values and integrity in the interpretation and communication of research results. Many professional societies, including the Society of Toxicology (<http://www.toxicology.org/ai/asot/ethics.asp>), have developed codes of ethics for their members. Conflict of interest has also been addressed by most publishers of toxicology journals (Krinsky and Sweet, 2009).



Table 2-1

Approximate Acute LD<sub>50</sub>s of Some Representative Chemical Agents

AGENT	LD <sub>50</sub> (mg/kg)*
Ethyl alcohol	10,000
Sodium chloride	4000
Ferrous sulfate	1500
Morphine sulfate	900
Phenobarbital sodium	150
Picrotoxin	5
Strychnine sulfate	2
Nicotine	1
D-Tubocurarine	0.5
Hemicholinium-3	0.2
Tetrodotoxin	0.10
Dioxin (TCDD)	0.001
Botulinum toxin	0.00001

\*LD<sub>50</sub> is the dosage (mg/kg body weight) causing death in 50% of exposed animals.

As the field of toxicology has matured and its influence on societal issues has increased, so has the need for the profession to make a commitment to examine the ethical, legal, and social implications of research and practice of toxicology.

## General Characteristics of the Toxic Response

One could define a poison as any agent capable of producing a deleterious response in a biological system, seriously injuring function or producing death. This is not, however, a useful working definition for the very simple reason that virtually every known chemical has the potential to produce injury or death if it is present in a sufficient amount. Paracelsus (1493–1541), a Swiss/German/Austrian physician, scientist, and philosopher, phrased this well when he noted, “What is there that is not poison? All things are poison and nothing [is] without poison. Solely the dose determines that a thing is not a poison.”

Among chemicals there is a wide spectrum of doses needed to produce deleterious effects, serious injury, or death. This is demonstrated in Table 2-1, which shows the dosage of chemicals needed to produce death in 50% of treated animals (lethal dose 50 [LD<sub>50</sub>]). Some chemicals produce death in microgram doses and are commonly thought of as being extremely poisonous. Other chemicals may be relatively harmless after doses in excess of several grams. It should be noted, however, that measures of acute lethality such as LD<sub>50</sub> do not accurately reflect the full spectrum of toxicity, or hazard, associated with exposure to a chemical. For example, some chemicals with low acute toxicity may have carcinogenic, teratogenic, or neurobehavioral effects at doses that produce no evidence of acute toxicity. In addition, there is growing recognition that genetic factors can account for individual susceptibility to a range of responses. Finally, it should be recognized that, for a given chemical, multiple different effects can occur in a given

organism, each with its own “dose–response relationship.” In some circumstances, effects that occur at low doses may not be evident at higher doses because other adverse responses overwhelm or mask more subtle effects that may occur at low doses. Although some have argued that such low-dose effects, not seen at higher doses, make the classical interpretation of the “dose–response” relationship no longer relevant, such low-dose effects also follow their own “dose–response” relationship, but with a “saturation” of the effect occurring at higher doses that induces other molecular, biochemical, and cellular effects that tend to obscure the effects seen at lower doses. The effects of exogenous chemicals that bind to and activate or inhibit endogenous hormone receptors (so-called endocrine disruptors—see Chap. 21) may often have “low-dose” effects that are quite different from those seen at much higher doses.

## CLASSIFICATION OF TOXIC AGENTS

Toxic agents are classified in a variety of ways, depending on the interests and needs of the classifier. In this textbook, for example, toxic agents are discussed in terms of their target organs (liver, kidney, hematopoietic system, etc), use (pesticide, solvent, food additive, etc), source (animal and plant toxins), and effects (cancer, mutation, liver injury, etc). The term *toxin* generally refers to toxic substances that are produced by biological systems such as plants, animals, fungi, or bacteria. The term *toxicant* is used in speaking of toxic substances that are produced by or are a by-product of anthropogenic (human-made) activities. Thus, zearalenone, produced by a mold, is a toxin, whereas “dioxin” (2,3,7,8-tetrachlorodibenzo-*p*-dioxin [TCDD]), produced during the production and/or combustion of certain chlorinated organic chemicals, is a toxicant. Some toxicants can be produced by both natural and anthropogenic activities. For example, polycyclic aromatic hydrocarbons are produced by the combustion of organic matter, which may occur both through natural processes (eg, forest fires) and through anthropogenic activities (eg, combustion of coal for energy production; cigarette smoking). Arsenic, a toxic metalloid, may occur as a natural contaminant of groundwater or may contaminate groundwater secondary to industrial activities. Generally, such toxic substances are referred to as toxicants, rather than toxins, because, although they are naturally produced, they are not produced by biological systems. Distinguishing a “toxin” from a “toxicant” is not always easy. For example, many pesticides, such as the pyrethroids, are synthetic analogs of natural products, such that one would call the pyrethrum found in the chrysanthemum flower a “toxin,” but the synthetic (and slightly altered in structure) form produced for use in pesticide formulations would be a “toxicant.” Thus, although technically incorrect, many physicians and others involved in the diagnosis and treatment of poisonings often use the term “toxin” to refer to any toxic substance, regardless of origin.

Toxic agents may also be classified in terms of their physical state (gas, dust, liquid, size, eg, nanotoxicology), their chemical stability or reactivity (explosive, flammable, oxidizer), general chemical structure (aromatic amine, halogenated hydrocarbon, etc), or poisoning potential (extremely toxic, very toxic, slightly toxic, etc). Classification of toxic agents on the basis of their biochemical mechanisms of action (eg, alkylating agent, cholinesterase inhibitor, endocrine disruptor) is usually more informative than classification by general terms such as irritants and corrosives. But more general classifications such as air pollutants, occupation-related agents, and acute and chronic poisons can provide a useful focus on a specific problem. It is evident from this discussion that no single classification is applicable to the entire spectrum of toxic agents and that a combination of classification systems or a classification based on



other factors is generally needed to provide the best characterization of a toxic substance. Nevertheless, classification systems that take into consideration both the chemical and the biological properties of an agent and the exposure characteristics are most likely to be useful for regulatory or control purposes and for toxicology in general.

## SPECTRUM OF UNDESIRABLE EFFECTS

The spectrum of undesired effects of chemicals is often broad. Some effects are deleterious and others are not. In therapeutics, for example, each drug produces a number of effects, but usually only one effect is associated with the primary objective of the therapy; all the other effects are referred to as *undesirable* or *side effects* of that drug for that therapeutic indication. However, some of these side effects may be desired for another therapeutic indication. For example, the "first generation" antihistamine diphenhydramine (Benadryl) is effective in reducing histamine responses associated with allergies, but it readily enters the brain and causes mild central nervous system (CNS) depression (drowsiness; delayed reaction time). With the advent of selective histamine receptor antagonists that do not cross the blood-brain barrier and thus do not have this CNS-depressant side effect, diphenhydramine is used less commonly today as an antihistamine. However, it is widely used as an "over-the-counter" sleep remedy, often in combination with analgesics (e.g., Tylenol PM, Excedrin PM), taking advantage of the CNS-depressant effects. Some side effects of drugs are never desirable and are always deleterious to the well-being of humans. These are referred to as the *adverse*, *deleterious*, or *toxic* effects of the drug.

## Allergic Reactions

*Chemical allergy* is an immunologically mediated adverse reaction to a chemical resulting from previous sensitization to that chemical or to a structurally similar one. The term *hypersensitivity* is most often used to describe this allergic state, but *allergic reaction* and *sensitization reaction* are also used to describe this situation when preexposure of the chemical is required to produce the toxic effect (see Chap. 12). Once sensitization has occurred, allergic reactions may result from exposure to relatively very low doses of chemicals; therefore, population-based dose-response curves for allergic reactions have seldom been obtained. Because of this omission, some people assumed that allergic reactions are not dose-related. Thus, they do not consider the allergic reaction to be a true toxic response. However, for a given allergic individual, allergic reactions are dose-related. For example, it is well known that the allergic response to pollen in sensitized individuals is related to the concentration of pollen in the air. In addition, because the allergic response is an undesirable, adverse, deleterious effect, it obviously is also a toxic response. Sensitization reactions are sometimes very severe and may be fatal.

Most chemicals and their metabolic products are not sufficiently large to be recognized by the immune system as a foreign substance and thus must first combine with an endogenous protein to form an antigen (or immunogen). A molecule that must combine with an endogenous protein to elicit an allergic reaction is called a *hapten*. The hapten-protein complex (antigen) is then capable of eliciting the formation of antibodies, and usually at least one or two weeks is required for the synthesis of significant amounts of antibodies. Subsequent exposure to the chemical results in an antigen-antibody interaction, which provokes the typical manifestations of allergy. The manifestations of allergy are numerous.

They may involve various organ systems and range in severity from minor skin disturbance to fatal anaphylactic shock. The pattern of allergic response differs in various species. In humans, involvement of the skin (e.g., dermatitis, urticaria, and itching) and involvement of the eyes (e.g., conjunctivitis) are most common, whereas in guinea pigs, bronchial constriction leading to asphyxia is the most common. However, chemically induced asthma (characterized by bronchial constriction) certainly does occur in some humans, and the incidence of allergic asthma has increased substantially in recent years. Hypersensitivity reactions are discussed in more detail in Chap. 12.

## Idiosyncratic Reactions

*Chemical idiosyncrasy* refers to a genetically determined abnormal reactivity to a chemical (Goldstein *et al.*, 1974; Lévesque, 1978; Deerecht, 2007). The response observed is usually qualitatively similar to that observed in all individuals but may take the form of extreme sensitivity to low doses or extreme insensitivity to high doses of the chemical. However, while some people use the term *idiosyncratic* as a catchall to refer to all reactions that occur with low frequency, it should not be used in that manner (Goldstein *et al.*, 1974). A classic example of an idiosyncratic reaction is provided by patients who exhibit prolonged muscular relaxation and apnea (inability to breathe) lasting several hours after a standard dose of succinylcholine. Succinylcholine usually produces skeletal muscle relaxation of only short duration because of its very rapid metabolic degradation by an enzyme that is present normally in the bloodstream called plasma butyrylcholinesterase (also referred to as pseudocholinesterase). Patients exhibiting this idiosyncratic reaction have a genetic polymorphism in the gene for the enzyme butyrylcholinesterase, which results in a protein that is less active in breaking down succinylcholine. Family pedigree and molecular genetic analyses have demonstrated that the presence of low plasma butyrylcholinesterase activity is due to the presence of one or more single-nucleotide polymorphisms (SNPs) in this gene (Bartels *et al.*, 1992). Similarly, there is a group of people who are abnormally sensitive to nitrites and certain other chemicals that have in common the ability to oxidize the iron in hemoglobin to produce *methemoglobin*, which is incapable of carrying oxygen to the tissues. The unusual phenotype is inherited as an autosomal recessive trait and is characterized by a deficiency in NADH-cytochrome *b<sub>5</sub>* reductase activity. The genetic basis for this idiosyncratic response has been identified as a single nucleotide change in codon 127, which results in replacement of serine with proline (Kobayashi *et al.*, 1990). The consequence of this genetic deficiency is that these individuals may suffer from a serious lack of oxygen delivery to tissues after exposure to doses of methemoglobin-producing chemicals that would be harmless to individuals with normal NADH-cytochrome *b<sub>5</sub>* reductase activity.

It is now recognized that many of the so-called idiosyncratic adverse drug reactions and many drug-drug interactions are due to specific genetic polymorphisms in drug-metabolizing enzymes, transporters, or receptors. As discussed previously, the growing field of pharmacogenomics and toxicogenomics has helped us identify the molecular basis for many previously described idiosyncratic responses to drugs and other toxic substances (Wang *et al.*, 2011). However, not all "idiosyncratic" responses to toxic substances are easily described by a single genetic polymorphism in a drug-metabolizing enzyme. It is generally thought that most, but not all, idiosyncratic drug responses are due to a combination of individual differences in the ability to: (1) form a reactive intermediate (usually through oxidation to an electrophilic intermediate); (2) detoxify



that reactive intermediate (usually through hydrolysis or conjugation), and/or (3) exhibit differences in immune response to adducted proteins (Uetrecht, 2007). The role of the immune system in mediating rare drug-induced toxic reactions in the liver, skin, and other organ systems is widely recognized, and specific genetic variants in certain parts of the genome that code for the major histocompatibility complexes (MHCs) give rise to specific immune responses to proteins that have been damaged by reactive intermediates of certain drugs. Thus, it is only the individuals who genetically form sufficient amounts of a reactive drug metabolite, and who then have an immune response to the modified protein, who have an adverse response to the drug (Uetrecht, 2007).

For example, troglitazone, introduced into the marketplace in 1997 as an effective treatment for type II diabetes, was subsequently withdrawn from the market because of a relatively rare (1 adverse response per 30,000 patients) but often fatal hepatotoxic response. Subsequent studies of tissues from patients who had developed hepatotoxic responses at the normal therapeutic doses revealed that individuals who lacked functional genes for 2 forms of glutathione S-transferase (GSTM1 and GSTT1) were more than 3 times as likely to develop troglitazone-induced hepatotoxicity than individuals with 1 or more functional GSTM1 or T1 genes (Ikeda, 2011). However, this does not explain the rarity of the adverse response, since there were many individuals who lacked GSTM1 and T1 genes who took troglitazone with no evident hepatotoxicity. Further studies have suggested that the idiosyncratic hepatotoxicity from troglitazone also has an immune system component, and genetic differences in specific human lymphocyte antigen (HLA) loci might contribute to idiosyncratic drug-induced hepatotoxicity (Ikeda, 2011).

## Immediate versus Delayed Toxicity

Immediate toxic effects can be defined as those that occur or develop rapidly after a single administration of a substance, whereas delayed toxic effects are those that occur after the lapse of some time. Carcinogenic effects of chemicals usually have a long latency period, often 20 to 30 years after the initial exposure, before tumors are observed in humans. For example, daughters of mothers who took diethylstilbestrol (DES) during pregnancy have a greatly increased risk of developing vaginal cancer, in young adulthood, approximately 20 to 30 years after their in utero exposure to DES (Hatch *et al.*, 1998). Also, delayed neurotoxicity is observed after exposure to some OP insecticides that act by covalent modification of an enzyme referred to as *neuropathy target esterase* (NTE), a neuronal protein with serine esterase activity (Glynn *et al.*, 1999). Binding of certain OP chemicals to this protein initiates degeneration of long axons in the peripheral and CNS. The most notorious of the compounds that produce this type of neurotoxic effect is triorthocresylphosphate (TOCP). The effect is not observed until at least several days after exposure to the toxic compound. In contrast, most substances produce immediate toxic effects but do not produce delayed effects.

## Reversible versus Irreversible Toxic Effects

Some toxic effects of chemicals are reversible, and others are irreversible. If a chemical produces pathological injury to a tissue, the ability of that tissue to regenerate largely determines whether the effect is reversible or irreversible. Thus, for a tissue such as liver, which has a high ability to regenerate, most injuries are reversible, whereas injury to the CNS is largely irreversible because differentiated cells of the CNS cannot divide and be replaced (although recovery from chemically induced damage to the CNS can occur,

primarily through the “plasticity” of the brain that allows developed neurons to learn new functions; see Chap. 16). Carcinogenic and teratogenic effects of chemicals, once they occur, are usually considered irreversible toxic effects.

## Local versus Systemic Toxicity

Another distinction between types of effects is made on the basis of the general site of action. Local effects are those that occur at the site of first contact between the biological system and the toxicant. Such effects are produced by the ingestion of caustic substances or the inhalation of irritant materials. For example, chlorine gas reacts with lung tissue at the site of contact, causing damage and swelling of the tissue, with possibly fatal consequences, even though very little of the chemical is absorbed into the bloodstream. The alternative to local effects is systemic effects. Systemic effects require absorption and distribution of a toxicant from its entry point to a distant site at which deleterious effects are produced. Most substances except highly reactive materials produce systemic effects. For some materials, both effects can be demonstrated. For example, tetraethyl lead produces effects on skin at the site of absorption and then is transported systemically to produce its typical effects on the CNS and other organs. If the local effect is marked, there may also be indirect systemic effects. For example, kidney damage after a severe acid burn is an indirect systemic effect because the toxicant does not reach the kidney.

Most chemicals that produce systemic toxicity do not cause a similar degree of toxicity in all organs; instead, they usually elicit their major toxicity in only 1 or 2 organs. These sites are referred to as the *target organs* of toxicity of a particular chemical. The target organ of toxicity is often not the site of the highest concentration of the chemical. For example, lead is concentrated in bone, but its toxicity is due to its effects in soft tissues, particularly the brain. DDT is concentrated in adipose tissue but produces no known toxic effects in that tissue.

The target organ of toxicity most frequently involved in systemic toxicity is the CNS (brain and spinal cord). Even with many compounds having a prominent effect elsewhere, damage to the CNS can be demonstrated by the use of appropriate and sensitive methods. Next in order of frequency of involvement in systemic toxicity are the circulatory system; the blood and hematopoietic system; visceral organs such as the liver, kidney, and lung; and the skin. Muscle and bone are least often the target tissues for systemic effects. With substances that have a predominantly local effect, the frequency with which tissues react depends largely on the portal of entry (skin, gastrointestinal tract, or respiratory tract).

## Interaction of Chemicals

Because of the large number of different chemicals an individual may come in contact with at any given time (workplace, drugs, diet, hobbies, etc), it is necessary, in assessing the spectrum of responses, to consider how different chemicals may interact with each other. Interactions can occur in a variety of ways. Chemical interactions are known to occur by a number of mechanisms, such as alterations in absorption, protein binding, and the biotransformation and excretion of 1 or both of the interacting toxicants. In addition to these modes of interaction, the response of the organism to combinations of toxicants may be increased or decreased because of toxicological responses at the site of action.

The effects of 2 chemicals given simultaneously produce a response that may simply be additive of their individual responses or may be greater or less than that expected by addition of their individual responses. The study of these interactions often leads to a



better understanding of the mechanism of toxicity of the chemicals involved. A number of terms have been used to describe pharmacological and toxicological interactions. An *additive* effect occurs when the combined effect of 2 chemicals is equal to the sum of the effects of each agent given alone (eg,  $2 + 3 = 5$ ). The effect most commonly observed when 2 chemicals are given together is an additive effect. For example, when 2 OP insecticides are given together, the cholinesterase inhibition is usually additive. A *synergistic* effect occurs when the combined effects of 2 chemicals are much greater than the sum of the effects of each agent given alone (eg,  $2 + 2 = 20$ ). For example, both carbon tetrachloride and ethanol are hepatotoxic compounds, but together they produce much more liver injury than the mathematical sum of their individual effects on liver at a given dose would suggest. *Potentiation* occurs when 1 substance does not have a toxic effect on a certain organ or system but when added to another chemical makes that chemical much more toxic (eg,  $0 + 2 = 10$ ). Isopropanol, for example, is not hepatotoxic, but when it is administered in addition to carbon tetrachloride, the hepatotoxicity of carbon tetrachloride is much greater than when it is given alone. *Antagonism* occurs when 2 chemicals administered together interfere with each other's actions or 1 interferes with the action of the other (eg,  $4 + 6 = 8$ ;  $4 + (-4) = 0$ ;  $4 + 0 = 1$ ). Antagonistic effects of chemicals are often very desirable in toxicology and are the basis of many antidotes. There are 4 major types of antagonism: functional, chemical, dispositional, and receptor. *Functional antagonism* occurs when 2 chemicals counterbalance each other by producing opposite effects on the same physiological function. For example, advantage is taken of this principle in that the blood pressure can markedly fall during severe barbiturate intoxication, which can be effectively antagonized by the intravenous administration of a vasopressor agent such as norepinephrine or metaraminol. Similarly, many chemicals, when given at toxic dose (TD) levels, produce convulsions, and the convulsions often can be controlled by giving anticonvulsants such as the benzodiazepines (eg, diazepam). *Chemical antagonism or inactivation* is simply a chemical reaction between 2 compounds that produces a less toxic product. For example, 2,3-dimercaptosuccinic acid (DMSA; Succimer) chelates with metal ions such as arsenic, mercury, and lead and decreases their toxicity. The use of antitoxins in the treatment of various animal toxins is also an example of chemical antagonism. The use of the strongly basic low-molecular-weight protein protamine sulfate to form a stable complex with heparin, which abolishes its anticoagulant activity, is another example. *Dispositional antagonism* occurs when the disposition—that is, the absorption, distribution, biotransformation, or excretion of a chemical—is altered so that the concentration and/or duration of the chemical at the target organ are diminished. Thus, the prevention of absorption of a toxicant by ipecac or charcoal and the increased excretion of a chemical by administration of an osmotic diuretic or alteration of the pH of the urine are examples of dispositional antagonism. If the parent compound is responsible for the toxicity of the chemical (such as the anticoagulant warfarin) and its metabolic breakdown products are less toxic than the parent compound, increasing the compound's biotransformation (metabolism) by administering a drug that increases the activity of the metabolizing enzymes (eg, a "microsomal enzyme inducer" such as phenobarbital) will decrease its toxicity. However, if the chemical's toxicity is largely due to a metabolic product (as in the case of the organophosphate insecticide parathion), inhibiting its biotransformation by an inhibitor of microsomal enzyme activity (SKF-525A or piperonyl butoxide) will decrease its toxicity. *Receptor antagonism* occurs when 2 chemicals that bind to the same receptor produce less of an effect when given together than the addition of their separate effects

(eg,  $4 + 6 = 8$ ) or when 1 chemical antagonizes the effect of the second chemical (eg,  $0 + 4 = 1$ ). Receptor antagonists are often termed *blockers*. This concept is used to advantage in the clinical treatment of poisoning. For example, the receptor antagonist naloxone is used to treat the respiratory depressive effects of morphine and other morphine-like narcotics by competitive binding to the same receptor. Another example of receptor antagonism is the use of the antiestrogen drug tamoxifen to lower breast cancer risk among women at high risk for this estrogen-related cancer. Tamoxifen competitively blocks estradiol from binding to its receptor. Treatment of organophosphate insecticide poisoning with atropine is an example not of the antidote competing with the poison for the receptor (cholinesterase) but of blocking the receptor (cholinergic receptor) for the excess acetylcholine that accumulates by poisoning of the cholinesterase by the organophosphate (see Chap. 22).

## Tolerance

Tolerance is a state of decreased responsiveness to a toxic effect of a chemical resulting from prior exposure to that chemical or to a structurally related chemical. Two major mechanisms are responsible for tolerance: 1 is due to a decreased amount of toxicant reaching the site where the toxic effect is produced (*dispositional tolerance*) and the other is due to a reduced responsiveness of a tissue to the chemical. Comparatively less is known about the cellular mechanisms responsible for altering the responsiveness of a tissue to a toxic chemical than is known about dispositional tolerance. Two chemicals known to produce dispositional tolerance are carbon tetrachloride and cadmium. The barbiturate, phenobarbital, produces tolerance to itself by increasing the expression of enzymes in the liver that are responsible for its biotransformation to pharmacologically inactive products, a process known as "biotransformation enzyme induction." The mechanism of cadmium tolerance is explained by induction of metallothionein, a metal-binding protein. Subsequent binding of cadmium to metallothionein rather than to critical cellular macromolecules decreases its toxicity.

## CHARACTERISTICS OF EXPOSURE

Toxic effects in a biological system are not produced by a chemical agent unless that agent or its metabolic breakdown (biotransformation) products reach appropriate sites in the body at a concentration and for a length of time sufficient to produce a toxic manifestation. Many chemicals are of relatively low toxicity in the "native" form but, when acted on by enzymes in the body, are converted to intermediate forms that interfere with normal cellular biochemistry and physiology. Thus, whether a toxic response occurs is dependent on the chemical and physical properties of the agent, the exposure situation, how the agent is metabolized by the system, the concentration of the active form at the particular target site(s), and the overall susceptibility of the biological system or subject. Thus, to characterize fully the potential hazard of a specific chemical agent, we need to know not only what type of effect it produces and the dose required to produce that effect but also information about the agent, the exposure, and its disposition by the subject. Two major factors that influence toxicity as it relates to the exposure situation for a specific chemical are the route of exposure and the duration and frequency of exposure.

## Route and Site of Exposure

The major routes (pathways) by which toxic agents gain access to the body are through the gastrointestinal tract (ingestion), the lungs (inhalation), or the skin (topical, percutaneous, or dermal). Toxic



agents generally produce the greatest effect and the most rapid response when given directly into the bloodstream (the intravenous route). An approximate descending order of effectiveness for the other routes would be inhalation, intraperitoneal, subcutaneous, intramuscular, intradermal, oral, and dermal. The "vehicle" (the material in which the chemical is dissolved) and other formulation factors can markedly alter absorption after ingestion, inhalation, or topical exposure. In addition, the route of administration can influence the toxicity of agents. For example, an agent that acts on the CNS, but is efficiently detoxified in the liver, would be expected to be less toxic when given orally than when given via inhalation, because the oral route requires that nearly all of the dose pass through the liver before reaching the systemic circulation and then the CNS.

Occupational exposure to toxic agents most frequently results from breathing contaminated air (inhalation) and/or direct and prolonged contact of the skin with the substance (dermal exposure), whereas accidental and suicidal poisoning occurs most frequently by oral ingestion. Comparison of the toxic dose (TD) of a toxic substance by different routes of exposure often provides useful information about its extent of absorption. In instances when the TD after oral or dermal administration is similar to the TD after intravenous administration, the assumption is that the toxic agent is absorbed readily and rapidly. Conversely, in cases where the TD by the dermal route is several orders of magnitude higher than the oral TD, it is likely that the skin provides an effective barrier to absorption of the agent. Toxic effects by any route of exposure can also be influenced by the concentration of the agent in its vehicle, the total volume of the vehicle and the properties of the vehicle to which the biological system is exposed, and the rate at which exposure occurs. Studies in which the concentration of a chemical in the blood is determined at various times after exposure are often needed to clarify the role of these and other factors in the toxicity of a compound. For more details on the absorption of toxicants, see Chap. 5.

## Duration and Frequency of Exposure

Toxicologists usually divide the exposure of experimental animals to chemicals into 4 categories: acute, subacute, subchronic, and chronic. Acute exposure is defined as exposure to a chemical for less than 24 hours, and examples of exposure routes are intraperitoneal, intravenous, and subcutaneous injection; oral intubation; and dermal application. Whereas acute exposure usually refers to a single administration, repeated exposures may be given within a 24-hour period for some slightly toxic or practically nontoxic chemicals. Acute exposure by inhalation refers to continuous exposure for less than 24 hours, most frequently for 4 hours. Repeated exposure is divided into 3 categories: subacute, subchronic, and chronic. *Subacute exposure* refers to repeated exposure to a chemical for 1 month or less, *subchronic* for 1 to 3 months, and *chronic* for more than 3 months, although usually this refers to studies with at least 1 year of repeated dosing. These 3 categories of repeated exposure can be by any route, but most often they occur by the oral route, with the chemical added directly to the diet.

In human exposure situations, the frequency and duration of exposure are usually not as clearly defined as in controlled animal studies, but many of the same terms are used to describe general exposure situations. Thus, workplace or environmental exposures may be described as *acute* (occurring from a single incident or episode), *subchronic* (occurring repeatedly over several weeks or months), or *chronic* (occurring repeatedly for many months or years).

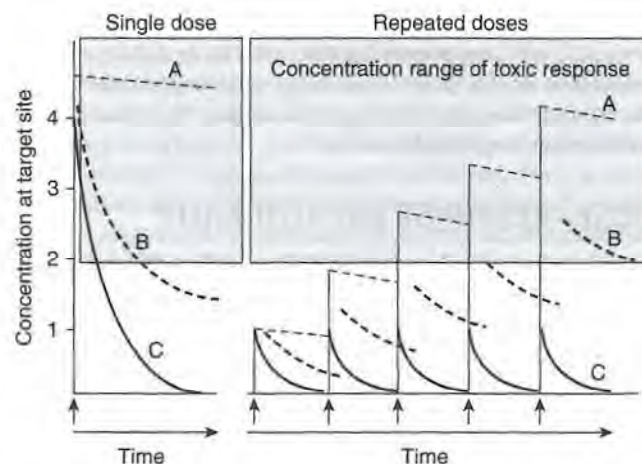


Figure 2-2. Diagrammatic view of the relationship between dose and concentration at the target site under different conditions of dose frequency and elimination rate. (Line A) A chemical with very slow elimination (eg, half-life of 1 year). (Line B) A chemical with a rate of elimination equal to frequency of dosing (eg, 1 day). (Line C) Rate of elimination faster than the dosing frequency (eg, 5 hours). Blue shaded area is representative of the concentration of chemical at the target site necessary to elicit a toxic response.

For many chemicals, the toxic effects that follow a single exposure are quite different from those produced by repeated exposure. For example, the primary acute toxic manifestation of benzene is CNS depression, but repeated exposures can result in bone marrow toxicity and an increased risk for leukemia. Acute exposure to chemicals that are rapidly absorbed is likely to produce immediate toxic effects but also can produce delayed toxicity that may or may not be similar to the toxic effects of chronic exposure. Conversely, chronic exposure to a toxic chemical may produce some immediate (acute) effects after each administration in addition to the long-term, low-level, or chronic effects of the toxic substance. In characterizing the toxicity of a specific chemical, it is evident that information is needed not only for the single-dose (acute) and long-term (chronic) effects but also for exposures of intermediate duration. The other time-related factor that is important in the temporal characterization of repeated exposures is the frequency of exposure. The relationship between elimination rate and frequency of exposure is shown in Fig. 2-2. A chemical that produces severe effects with a single dose may have no effect if the same total dose is given in several intervals. For the chemical depicted by line B in Fig. 2-2, in which the half-life for elimination (time necessary for 50% of the chemical to be removed from the bloodstream) is approximately equal to the dosing frequency, a theoretical toxic concentration (shown conceptually as 2 concentration units in Fig. 2-2) is not reached until the fourth dose, whereas that concentration is reached with only 2 doses for chemical A, which has an elimination rate much slower than the dosing interval (time between each repeated dose). Conversely, for chemical C, where the elimination rate is much shorter than the dosing interval, a toxic concentration at the site of toxic effect will never be reached regardless of how many doses are administered. Of course, it is possible that residual cell or tissue damage occurs with each dose even though the chemical itself is not accumulating. The important consideration, then, is whether the interval between doses is sufficient to allow for complete repair of tissue damage. It is evident that with any type of repeated exposure, the production of a toxic effect not only is influenced by the frequency of exposure but may also, in fact, be totally dependent on the frequency rather than the duration of exposure. Chronic toxic effects may occur, therefore, if the chemical accumulates in the biological system (rate



of absorption exceeds the rate of biotransformation and/or excretion), if it produces irreversible toxic effects, or if there is insufficient time for the system to recover from the toxic damage within the exposure frequency interval. For additional discussion of these relationships, see Chaps. 5 and 7.

## DOSE-RESPONSE RELATIONSHIP

The characteristics of exposure and the spectrum of toxic effects come together in a correlative relationship customarily referred to as the *dose-response relationship*. Whatever response is selected for measurement, the relationship between the degree of response of the biological system and the amount of toxicant administered assumes a form that occurs so consistently as to be considered the most fundamental and pervasive concept in toxicology.

From a practical perspective, there are 2 types of dose-response relationships: (1) the individual dose-response relationship, which describes the response of an *individual* organism to varying doses of a chemical, often referred to as a "graded" response because the measured effect is continuous over a range of doses, and (2) a quantal dose-response relationship, which characterizes the distribution of individual responses to different doses in a *population* of individual organisms. It is also important to recognize that a given chemical may have multiple different molecular, biochemical, and cellular effects, each with its own "dose-response" relationship. Thus, the nature of a toxic response might very well be different at low doses than at higher doses. In the case of population-level "dose-response" characterization, the observed response is an integration of multiple individual "dose-response relationships" occurring in different cell types, and at different molecular sites within those cells. Subtle effects that occur at low doses may be masked or overwhelmed by more evident responses occurring at higher doses.

### Individual, or Graded, Dose-Response Relationships

Individual dose-response relationships are characterized by a dose-related increase in the severity of the response. The dose relatedness of the response often results from an alteration of a specific biochemical process. For example, Fig. 2-3 shows the dose-response relationship between different dietary doses of the organophosphate insecticide chlorpyrifos and the extent of inhibition of 2 different enzymes in the brain and liver: acetylcholinesterase and carboxylesterase. In the brain, the degree of inhibition of both enzymes is clearly dose-related and spans a wide range, although the amount of inhibition per unit dose is different for the 2 enzymes. From the shapes of these 2 dose-response curves it is evident that, in the brain, cholinesterase is more easily inhibited than carboxylesterase. The toxicological response that results is directly related to the degree of cholinesterase enzyme inhibition in the brain. Thus, clinical signs and symptoms for chlorpyrifos would follow a dose-response relationship similar to that for brain cholinesterase. However, as noted above, for many chemicals, more than 1 effect may result because of multiple different target sites in different tissues. Thus, the observed response to varying doses of a chemical in the whole organism is often complicated by the fact that most toxic substances have multiple sites or mechanisms of toxicity, each with its own "dose-response" relationship and subsequent adverse effect. Note that when these dose-response data are plotted using the base 10 log of the dose on the abscissa (Fig. 2.3B), a better "fit" of the data to a straight line usually occurs. This is typical of many graded as well as quantal dose-response relationships.

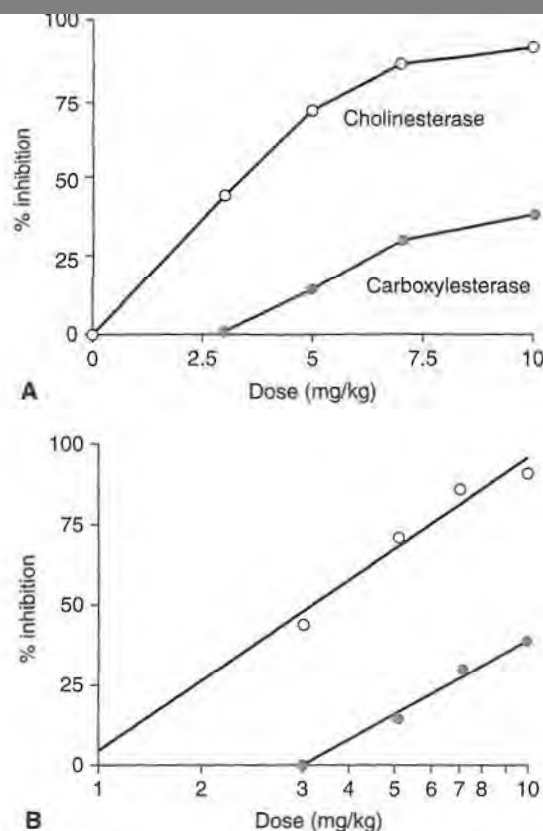


Figure 2-3. Dose-response relationship between different doses of the organophosphate insecticide chlorpyrifos and esterase enzyme inhibition in the brain. Open circles and blue lines represent acetylcholinesterase activity and closed circles represent carboxylesterase activity in the brains of pregnant female Long-Evans rats given 5 daily doses of chlorpyrifos. (A) Dose-response curve plotted on an arithmetic scale. (B) Same data plotted on a semi-log scale. (Data from Lassiter *et al.*, 1999, with permission.)

### Quantal Dose-Response Relationships

In contrast to the "graded" or continuous-scale dose-response relationship that occurs in individuals, the dose-response relationships in a *population* are by definition quantal—or "all or none"—in nature, that is, at any given dose, an individual in the population is classified as either a "responder" or a "nonresponder." Although these distinctions of "quantal population" and "graded individual" dose-response relationships are useful, the 2 types of responses are conceptually identical. The ordinate in both cases is simply labeled *the response*, which may be the degree of response in an individual or system or the fraction of a population responding, and the abscissa is the range in administered doses.

A widely used statistical approach for estimating the response of a population to a toxic exposure is the "effective dose" (ED). Generally, the midpoint, or 50%, response level is used, giving rise to the "ED<sub>50</sub>" value. However, any response level, such as an ED<sub>01</sub>, ED<sub>10</sub>, or ED<sub>30</sub>, could be chosen. A graphical representation of an approximate ED<sub>50</sub> is shown in Fig. 2-4. Note that these data are "quantal." Where death is the measured end point, the ED<sub>50</sub> would be referred to as the LD<sub>50</sub>. Historically, determination of the LD<sub>50</sub> was often the first experiment performed with a new chemical. Today, it is widely recognized that the LD<sub>50</sub> is of marginal value as a measure of hazard, although it does provide a useful "ball park" indication of the relative hazard of a compound to cause serious, life-threatening poisoning from a single exposure. Although death is an obvious quantal end point to measure, it should be noted that any



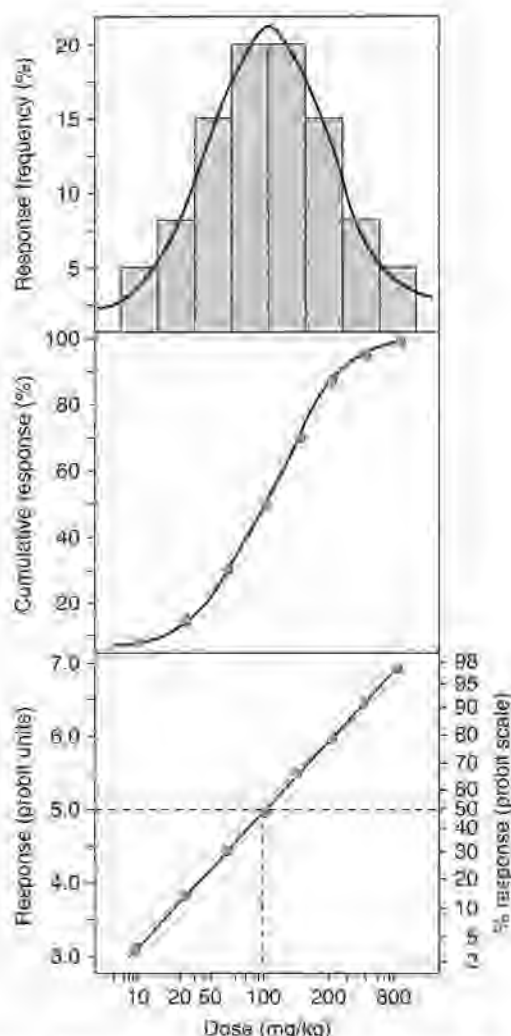


Figure 2-4. Diagram of quantal dose-response relationship. The abscissa is a log dosage of the chemical. In the top panel the ordinate is response frequency, in the middle panel the ordinate is percent response, and in the bottom panel the response is in probit units (see text).

quantal response could be used. For example, the  $LD_{50}$  of lead or DDT is not a relevant end point when characterizing hazards of the agents to children or wildlife, respectively. Even continuous variables can be converted to quantal responses if desired. For example, an antihypertensive drug that lowers blood pressure might be evaluated in a population by assigning a "responder" as an individual whose blood pressure was lowered by 10 mm Hg or more. Note that, in this example, an individual who responded to a change in blood pressure of 50 mm Hg would be classified the same as an individual with a change in only 10 mm Hg, yet an individual with a change in 8 mm Hg would be classified as a "nonresponder." The top panel of Fig. 2-4 shows that quantal dose responses typically exhibit a normal or Gaussian distribution. The frequency histogram in this panel also shows the relationship between dose and effect. The bars represent the percentage of animals that responded at each dose minus the percentage that responded at the immediately lower dose. One can clearly see that only a few animals responded to the lowest dose and the highest dose. Larger numbers of animals responded to doses intermediate between these 2 extremes, and the maximum frequency of response occurred in the middle portion of the dose range. Thus, we have a bell-shaped curve known as a *normal frequency distribution*. The reason for this normal distribution is that there are

differences in susceptibility to chemicals among individuals; this is known as biological variation. Animals responding at the left end of the curve are referred to as *hypersusceptible*, and those at the right end of the curve are called *resistant*. If the numbers of individuals responding at each consecutive dose are added together, a cumulative, quantal dose-response relationship is obtained. When a sufficiently large number of doses is used with a large number of animals per dose, a sigmoid dose-response curve is observed, as depicted in the middle panel of Fig. 2-4. With the lowest dose (6 mg/kg), 1% of the animals respond. A normally distributed sigmoid curve such as this one approaches a response of 0% as the dose is decreased and approaches 100% as the dose is increased, but—*theoretically*—it never passes through 0% and 100%. However, the minimally ED of any chemical that evokes a stated all-or-none response is called the *threshold dose* even though it cannot be determined experimentally.

For a normally distributed population response, the sigmoid curve has a relatively linear portion between 16% and 84%. These values represent the limits of 1 standard deviation (SD) of the mean (and the median) in a population with truly normal or Gaussian distribution. However, it is usually not practical to describe the dose-response curve from this type of plot because one does not usually have large enough sample sizes to define the sigmoid curve adequately. In a normally distributed population, the mean  $\pm 1$  SD represents 68.3% of the population, the mean  $\pm 2$  SD represents 95.5% of the population, and the mean  $\pm 3$  SD equals 99.7% of the population. Because quantal dose-response phenomena are usually normally distributed, one can convert the percent response to units of deviation from the mean or normal equivalent deviations (NEDs). Thus, the NED for a 50% response is 0; an NED of +1 is equated with an 84.1% response. Traditionally, units of NED are converted by the addition of 5 to the value to avoid negative numbers; these converted units are called *probit units* (Bliss, 1957). The probit (from the contraction of *probability unit*), then, is an NED plus 5. In this transformation, a 50% response becomes a probit of 5; a +1 deviation becomes a probit of 6, and a -1 deviation is a probit of 4.

The data given in the top 2 panels of Fig. 2-4 are replotted in the bottom panel with the response plotted in probit units. The data in the middle panel (which was in the form of a sigmoid curve) and the top panel (a bell-shaped curve) form a straight line when transformed into probit units. In essence, what is accomplished in a probit transformation is an adjustment of quantal data to an assumed normal population distribution, resulting in a straight line. The  $ED_{50}$  is obtained by drawing a horizontal line from the probit unit 5, which is the 50% response point, to the dose-effect line. At the point of intersection, a vertical line is drawn, and this line intersects the abscissa at the  $ED_{50}$  point. It is evident from the line that information with respect to the ED for 90% or for 10% of the population also may be derived by a similar procedure. Mathematically, it can be demonstrated that the range of values encompassed by the confidence limits is narrowest at the midpoint of the line ( $ED_{50}$ ) and widest at both extremes ( $ED_{10}$  and  $ED_{90}$ ) of the dose-response curve (dotted lines in Fig. 2-5). In addition to the  $ED_{50}$ , the slope of the dose-response curve can also be obtained. Fig. 2-5 demonstrates the dose-response curves for the response of 2 compounds. Compound A exhibits a "flat" dose-response curve, showing that a large change in dosage is required before a significant change in response will be observed. However, compound B exhibits a "steep" dose-response curve, where a relatively small change in dosage will cause a large change in response. It is evident that the  $ED_{50}$  for both compounds is the same (8 mg/kg). However, the slopes of the dose-response curves are quite different. At one half of  $ED_{50}$  of the compounds (4 mg/kg), less than 1% of the animals exposed to compound B would respond but 20% of the animals given compound A would respond.



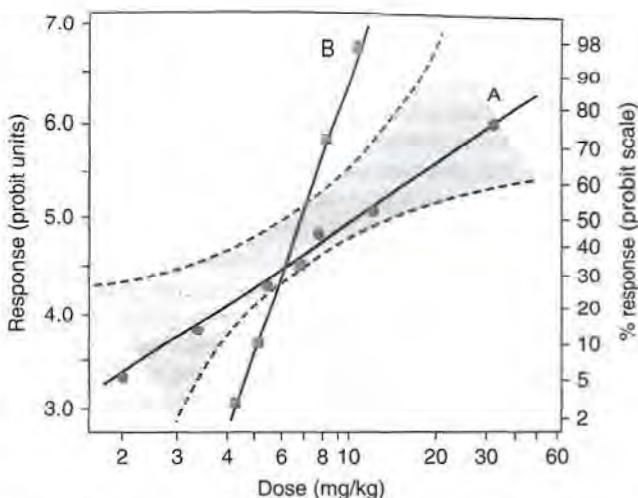


Figure 2-5. Comparison of dose-response relationship for 2 different chemicals, plotted on a log dose-probit scale. Note that the slope of the dose-response is steeper for chemical B than for chemical A. Dotted lines represent the confidence limits for chemical A.

In Figs. 2-4 and 2-5 the dosage has been given on a log basis. Although the use of the log of the dosage is empiric, log dosage plots for normally distributed quantal data provide a more nearly linear representation of the data. It must be remembered, however, that this is not universally the case. Some radiation effects, for example, give a better probit fit when the dose is expressed arithmetically rather than logarithmically. There are other situations in which other functions (eg, exponentials) of dosage provide a better fit to the data than does the log function. It is also conventional to express the dosage in milligrams per kilogram. It might be argued that expression of dosage on a mole-per-kilogram basis would be better, particularly for making comparisons among a series of compounds. Although such an argument has considerable merit, dosage is usually expressed in milligrams per kilogram.

One might also view dosage on the basis of body weight as being less appropriate than other bases, such as surface area. The term *allometry* refers to the field of study that examines the relationships between body weight and other biological and physical parameters such as rate of basal metabolism (caloric consumption),

heart rate, blood flow, etc. Allometric studies revealed that the relationship between body weight and various other physiological parameters can be closely estimated by the following formula:  $Y = aW^b$ , where  $Y$  is the biological parameter of interest and  $a$  and  $b$  are constants that relate  $Y$  to body weight (Rodricks *et al.*, 2008). In general, organ sizes between species seem to scale best when  $b$  is equal to 1, whereas metabolically derived parameters scale better when  $b$  is 0.67 to 0.75. The relationship between body surface area and body weight across most mammalian species is closely described by the formula  $SA = 10.5 \times (\text{body weight [grams]})^{0.67}$  (Harkness and Wagner, 1995). Empirical comparisons of toxicity data across species confirm that this relationship is appropriate for toxicological scaling. For example, Travis and White (1988) analyzed a number of toxicity testing data sets for 27 different chemotherapeutic drugs for which toxicity data were available in mouse, rat, hamster, dog, monkey, and human. They found that the exponent of body weight that gave the best correlation with toxicity was 0.73, with 95% confidence bounds of 0.69 to 0.77 (Rodricks *et al.*, 2008). Table 2-2 illustrates the differences in comparative doses when scaling is done by body weight (mg/kg) versus an allometric approach that uses an exponent of either 0.67 or 0.75. Thus, if a scaling factor of  $(BW)^{2/3}$  is used, a mouse would need to receive a dose 13 times greater than that required for humans for an equivalent toxic response, whereas the dose would be 7 times greater if a scaling factor of  $(BW)^{3/4}$  was used. However, not all toxic responses will necessarily scale across species in the same way. For example, acute lethality seemed to correlate better across species when body weight, rather than body surface area, was used (Rhomberg and Wolff, 1998). The selection of the most appropriate scaling factor should also take into account pharmacokinetic differences, including physiologically based pharmacokinetic modeling (PBPK). When toxicity is attributable to the formation of a toxic metabolite, or when xenobiotic biotransformation is saturated at high doses, a scaling factor of 1 may be more appropriate than 0.75 (Kirman *et al.*, 2003).

## Shape of the Dose-Response Curve

**Essential Nutrients** The shape of the dose-response relationship has many important implications in toxicity assessment. For example, for substances that are required for normal physiological

Table 2-2

### Allometric Scaling of Dose Across Different Species

SPECIES	WEIGHT (kg)	SURFACE AREA (cm <sup>2</sup> ) <sup>a</sup>	FOLD DIFFERENCE, RELATIVE TO HUMANS, NORMALIZED BY BODY WEIGHT		
			mg/kg	(BW) <sup>2/3</sup>	(BW) <sup>3/4</sup>
Mouse	0.30	103	1	13.0	7.0
Rat	0.2	365	1	6.9	4.3
Guinea pig	0.4	582	1	5.5	3.6
Rabbit	1.5	1410	1	3.5	2.6
Cat	2	1710	1	3.2	2.4
Monkey	4	2720	1	2.6	2.0
Dog	12	5680	1	1.8	1.5
Human	70	18,500	1	1.0	1.0

<sup>a</sup>Surface area of animals is closely approximated by the following formula:  $SA = 10.5 \times (\text{body weight [grams]})^{2/3}$ .



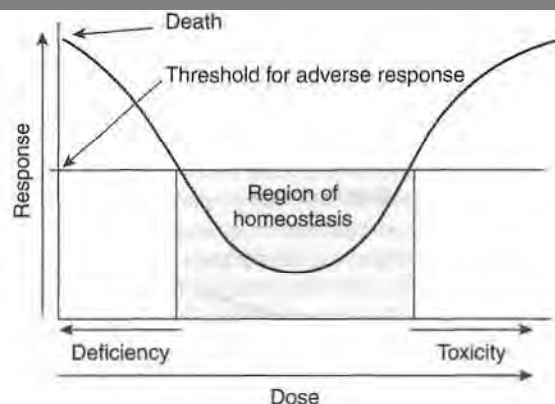


Figure 2-6. Individual dose-response relationship for an essential substance such as a vitamin or trace element. It is generally recognized that, for most types of toxic responses, a threshold exists such that at doses below the threshold, no toxicity is evident. For essential substances, doses below the minimum daily requirement, as well as those above the threshold for safety, may be associated with toxic effects. The blue shaded region represents the "region of homeostasis"—the dose range that results in neither deficiency nor toxicity.

function and survival (eg, vitamins and essential trace elements such as chromium, cobalt, and selenium), the "graded" dose-response relationship in an individual over the entire dose range is actually U-shaped (Fig. 2-6). That is, at very low doses, there is a high level of adverse effect, which decreases with an increasing dose. This region of the dose-response relationship for essential nutrients is commonly referred to as a *deficiency*. As the dose is increased to a point where the deficiency no longer exists, no adverse response is detected and the organism is in a state of homeostasis. However, as the dose is increased to abnormally high levels, an adverse response (usually qualitatively different from that observed at deficient doses) appears and increases in magnitude with increasing dose, just as with other toxic substances. Thus, it is recognized that high doses of vitamin A can cause liver toxicity and birth defects, high doses of selenium can affect the brain, and high doses of estrogens may increase the risk of breast cancer, even though low doses of all these substances are essential for life.

**Hormesis** There is considerable evidence to suggest that some nonnutritional toxic substances may also impart beneficial or stimulatory effects at low doses but that, at higher doses, they produce adverse effects. This concept of "hormesis" was first described for radiation effects but may also pertain to most chemical responses (Calabrese and Blaine, 2005). Thus, in plotting dose versus response over a wide range of doses, the effects of hormesis may also result in a "U-shaped" dose-response curve. In its original development, the concept of hormesis pertained to the ability of substances to stimulate biological systems at low doses but to inhibit them at high doses. The application of the concept of hormesis to whole-animal toxicological dose-response relationships may also be relevant but requires that the "response" on the ordinate be variant with dose. For example, chronic alcohol consumption is well recognized to increase the risk of esophageal cancer, liver cancer, and cirrhosis of the liver at relatively high doses, and this response is dose-related (curve A, Fig. 2-7). However, there is also substantial clinical and epidemiological evidence that low to moderate consumption of alcohol reduces the incidence of coronary heart disease and stroke (curve B, Fig. 2-7) (Hanna *et al.*, 1997). Thus, when all responses are plotted on the ordinate, a "U-shaped" dose-response curve is obtained (curve C, Fig. 2-7). U-shaped dose-response relationships

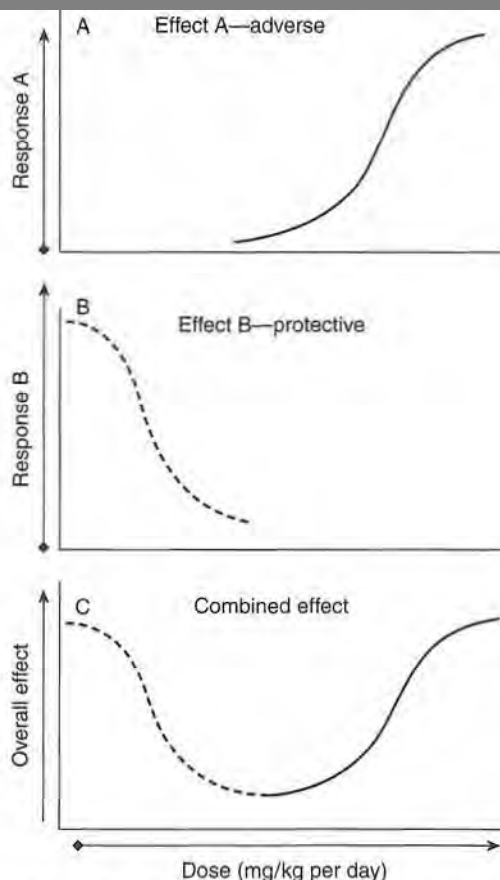


Figure 2-7. Hypothetical dose-response relationship depicting characteristics of hormesis. Hormetic effects of a substance are hypothesized to occur when relatively low doses result in the stimulation of a beneficial or protective response (B), such as induction of enzymatic pathways that protect against oxidative stress. Although low doses provide a potential beneficial effect, a threshold is exceeded as the dose increases and the net effects will be detrimental (A), resulting in a typical dose-related increase in toxicity. The complete dose-response curve (C) is conceptually similar to the individual dose-response relationship for essential nutrients shown in Fig. 2-6.

have obvious implications for the process of low-dose extrapolation in risk assessment.

**Threshold** Another important aspect of the dose-response relationship at low doses is the concept of the threshold. It has long been recognized that acute toxicological responses are associated with thresholds, that is, there is some dose below which the probability of an individual responding is zero. Obviously, the identification of a threshold depends on the particular response that is measured, the sensitivity of the measurement, and the number of subjects studied. For the individual dose-response relationship, thresholds for most toxic effects certainly exist, although interindividual variability in response and qualitative changes in response pattern with dose make it difficult to establish a true "no effects" threshold for any chemical. The biological basis of thresholds for acute responses is well established and frequently can be demonstrated on the basis of mechanistic information (Aldridge, 1986). The traditional approaches to establishing acceptable levels of exposure to chemicals are inherently different for threshold versus nonthreshold responses. The existence of thresholds for chronic responses is less well defined, especially in the area of chemical carcinogenesis. It is, of course, impossible to scientifically prove the absence of a threshold, as one can never prove a negative.



Nevertheless, for the identification of “safe” levels of exposure to a substance, the absence or presence of a threshold is important for practical reasons (see Chap. 4). A classic example of the difficulty of establishing thresholds experimentally is provided by the “ED<sub>01</sub>” study, where over 24,000 mice and 81 different treatment groups were used to determine the shape of the dose–response relationship for the prototypical carcinogen 2-acetylaminofluorene (2-AAF). The study was designed to identify a statistically significant response of 1% (0.01 probability). The mice were exposed to 2-AAF at 1 of 7 different doses in the dose range of 30 to 150 ppm (plus 0 dose control) (Littlefield *et al.*, 1979). Eight “sacrifice intervals” were used to determine how quickly tumors developed. Both types of tumors demonstrated increasing incidence with increasing dose, but the shapes of the 2 curves are dramatically different. For liver tumors, no clear threshold was evident, whereas for bladder tumors, an apparent threshold was evident. However, the apparent threshold, or “no observable adverse effect level” (NOAEL), for bladder cancer was lower at 33 months (45 ppm) than at 24 months (75 ppm). Of course, the ability to detect a low incidence of tumors depends on the number of animals used in the study. Thus, although a threshold (a dose below which no response occurs) appears evident for bladder tumors, one cannot say for certain that tumors would not occur if more animals had been included in the lower-dose groups. A different animal model that relies on relatively brief exposure of rainbow trout embryos to carcinogens has allowed an even more statistically stringent analysis of the shape of the dose–response curve at low doses for mutagenic carcinogens. Using this model with 2 different genotoxic carcinogens, dibenzo[*d,e,f*,*p*]chrysene (DBC, also referred to as dibenzo[*a,l*]pyrene) and aflatoxin B<sub>1</sub> (AFB<sub>1</sub>), estimates of the shape of the dose–response curve down to a response level of 1 additional tumor in 5000 animals could be obtained, because very large numbers of animals could be exposed. In both studies, over 40,000 trout were exposed to different doses ranging over a factor of 200 (AFB<sub>1</sub>, lowest dose 0.5 ppb, highest dose 110 ppb) to 500 (DBC, lowest dose 0.45 ppm, highest dose 225 ppm), with over 8000 animals in the control and low-dose groups (Williams, 2012). Both of these chemicals are potent mutagens, so it was assumed that both the rate of DNA adduct formation and the tumor incidence would be linear throughout the dose range. However, for DBC, there was a clear deviation from linearity at the lower doses, such that the extrapolated dose–response curve crossed the y-axis at 1 cancer in a million exposed animals at a dose 500- to 1500-fold (depending on the statistical model) higher than would have been predicted from the linear extrapolation below the 10% response range (ED<sub>10</sub>) (Bailey *et al.*, 2009) (Fig. 2-8). Remarkably, although the tumor response exhibited a clear “threshold,” the formation of DBC–DNA adducts was quite linear through the lowest dose used. In contrast, in a similarly designed study using the potent carcinogen, AFB<sub>1</sub>, both tumor response and AFB–DNA adduct formation appear approximately linear down through the lowest dose; the liver tumor response to AFB<sub>1</sub> remained linear to the lowest dose, although the slope was about 1.5 and the predicted dose resulting in 1 cancer in a million exposed animals was about 10-fold higher than that predicted from the extrapolated LED<sub>10</sub> line, although the lowest doses tested yielded tumor incidence that was close (within a factor of 2) to the background tumor rate (Fig. 2-9) (Williams *et al.*, 2009a; Williams, 2012).

(See Chap. 4 for more discussion on statistical issues related to extrapolation of dose–response curves and the determination of NOAELs.)

In evaluating the shape of the dose–response relationship in populations, it is realistic to consider inflections in the shape of the dose–response curve rather than absolute thresholds. That is, the

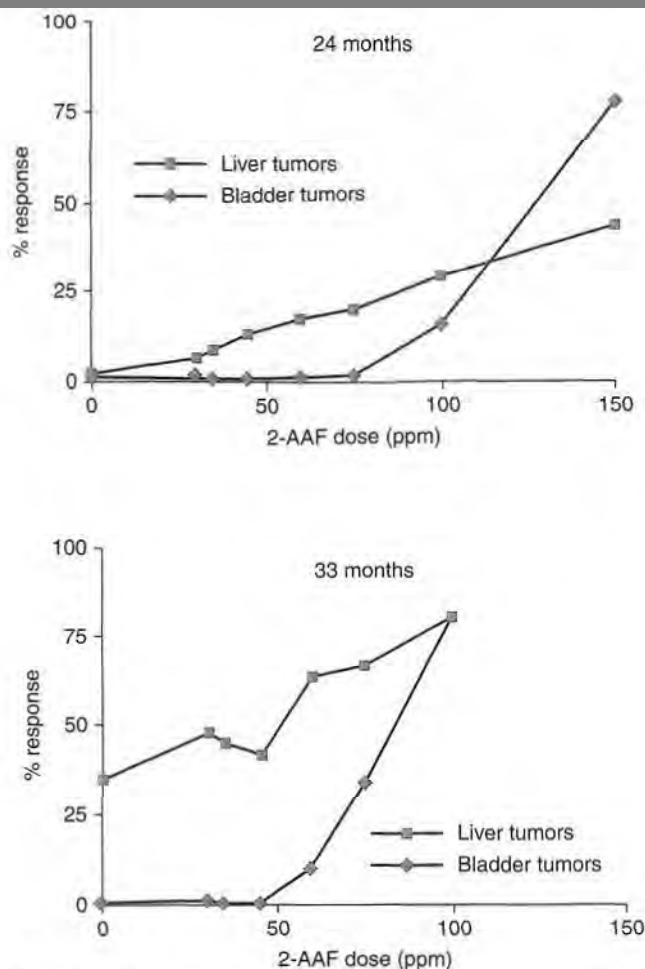


Figure 2-8. Dose–response relationship for carcinogens—rodents and 2-AAF.

slope of the dose–response relationship at high doses may be substantially different from the slope at low doses, usually because of dispositional differences in the chemical. Saturation of biotransformation pathways, protein-binding sites or receptors, and depletion of intracellular cofactors represent some reasons why sharp inflections in the dose–response relationship may occur. For example, the widely used analgesic acetaminophen has a very low rate of liver toxicity at normal therapeutic doses. Even though a toxic metabolite (*N*-acetyl-*p*-benzoquinone imine [NAPQI]) is produced in the liver

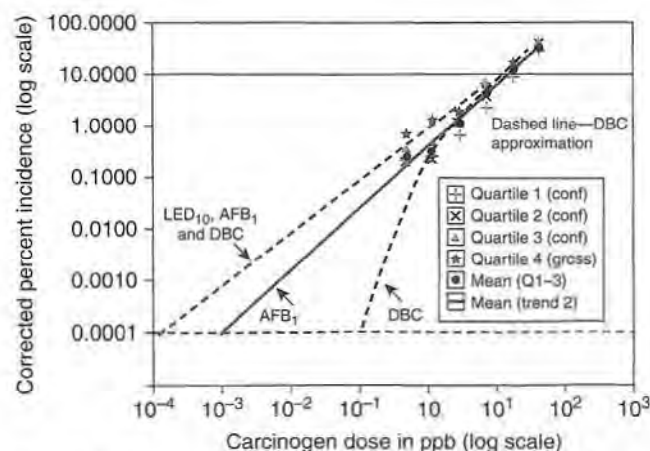


Figure 2-9. Dose–response relationship for carcinogens—fish and aflatoxin B<sub>1</sub>. (Reproduced with permission from Williams, 2012.)



at therapeutic doses, it is rapidly detoxified through conjugation with the intracellular antioxidant glutathione. However, at very high doses, the level of intracellular glutathione in the liver is depleted and NAPQI accumulates, causing serious and potentially fatal liver toxicity. This effect is analogous to the rapid change in pH of a buffered solution that occurs when the buffer capacity is exceeded. Some toxic responses, most notably the development of cancer after the administration of genotoxic carcinogens, are often considered to be linear at low doses and thus do not exhibit a threshold. In such circumstances, there is no dose with "zero" risk, although the risk decreases proportionately with a decrease in the dose. The existence or lack of existence of a threshold dose for carcinogens has many regulatory implications and is a point of considerable controversy and research in the field of quantitative risk assessment for chemical carcinogens (see Chap. 4).

**Nonmonotonic Dose-Response Curves** For chemicals that exert their primary toxic effects via modification of hormonal responses (endocrine disruptors), it is possible that effects occur at relatively low doses that are not seen at higher doses, thereby seemingly defying the traditional concept of "dose-response".

The characterization of so-called nonmonotonic dose-response (NMDR) curves is an important refinement in our understanding of dose-response relationships in toxicology (Fig. 2-10). Indeed, some chemicals, such as the plastics monomer bisphenol A (BPA), exhibit relatively little evident toxicity at high doses in traditional acute toxicity testing procedures, yet may have important biological effects when exposure occurs during sensitive periods of development, even at doses well below those shown to cause evident toxicity. For example, human pituitary cells cultured in the presence of BPA elicited significant responses at concentrations of 0.001 and

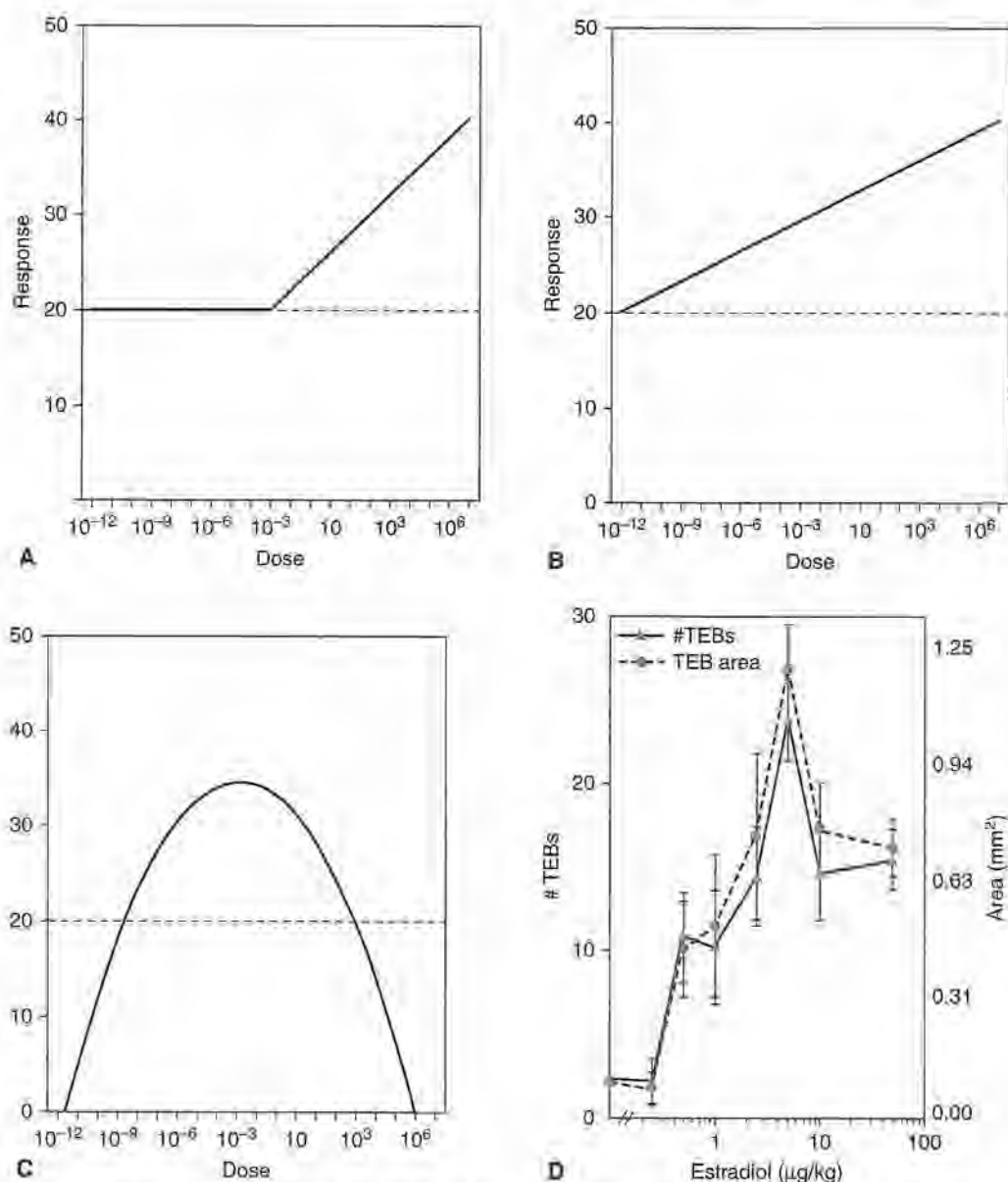


Figure 2-10. Hypothetical dose-response curves for the (A) threshold responses, (B) nonthreshold linear response, and (C and D) nonmonotonic dose-response (NMDR). Curves A and B reflect traditional dose-response relationships. However, in the NMDR curve (C), an increase in dose does not necessarily correspond to an increase in response, such that, in this example, doses from  $10^{-12}$  to  $10^{-1}$  dose units result in an increase in response, and doses from  $10^{-1}$  to  $10^6$  dose units result in a decrease in response. Curve D represents the NMDR curves observed in mammary gland morphological parameters after administration of estradiol to ovariectomized females. The left y-axis is the number of terminal end buds (TEBs), and the right y-axis is total area of all TEBs; the TEB is an estrogen-dependent structure. (Based on Vandenberg *et al.*, 2009.)



0.01 nM, but not at 1 and 10 nM, yet the response was seen at 100 nM (Vandenberg *et al.*, 2009). Several other studies have found that BPA and other endocrine-active xenobiotics can elicit NMDR relationships for a variety of other specific receptors and/or cell signaling pathways (reviewed in Vandenberg *et al.*, 2009).

Specific cellular/molecular mechanisms that might explain NMDR curves include: (1) upregulation of some receptors at low concentrations, with downregulation of the same receptors at higher levels, and/or (2) integration of 2 or more monotonic dose-response curves that occur through different molecular/cellular pathways with common end points but opposite effects (Vandenberg *et al.*, 2009). Since endocrine-active xenobiotics may act as weak agonists for specific hormone receptors, it is reasonable that low doses could have different effects than high doses if, as partial agonists, they competitively inhibit endogenous ligands at higher concentrations, but have either no or positive agonist effects at low concentrations. Another explanation for NMDR curves is that we simply do not understand all the varied and interconnected molecular pathways that work in concert to produce an observable response at the organismal level. Indeed, BPA has been shown to have multiple different effects on a myriad of putative molecular pathways involved in hormone function, so it perhaps is not surprising to see NMDR functions over dose ranges of many orders of magnitude (Vandenberg *et al.*, 2009).

## Assumptions in Deriving the Dose-Response Relationship

A number of assumptions must be considered before dose-response relationships can be used appropriately. The first is that the response is due to the chemical administered. To describe the relationship between a toxic material and an observed effect or response, one must know with reasonable certainty that the relationship is indeed a causal one. For some data, it is not always apparent that the response is a result of chemical exposure. For example, an epidemiological study might result in the discovery of an "association" between a response (eg, disease) and 1 or more variables. Frequently, the data are presented similarly to the presentation of "dose response" in pharmacology and toxicology. Use of the dose response in this context is suspect unless other convincing evidence supports a causal connection between the estimated dose and the measured end point (response). Unfortunately, in nearly all retrospective and case-control studies and even in many prospective studies, the dose, duration, frequency, and routes of exposure are seldom quantified, and other potential etiologic factors are frequently present. In its most strict usage, then, the dose-response relationship is based on the knowledge that the effect is a result of a known toxic agent or agents.

A second assumption seems simple and obvious: the magnitude of the response is in fact related to the dose. Perhaps because of its apparent simplicity, this assumption is often a source of misunderstanding. It is really a composite of 3 other assumptions that recur frequently:

1. There is a molecular target site (or sites) with which the chemical interacts to initiate the response.
2. The production of a response and the degree of response are related to the concentration of the chemical at the target site.
3. The concentration at the site is, in turn, related to the dose administered.

The third assumption in using the dose-response relationship is that there exist both a quantifiable method of measuring and a precise means of expressing the toxicity. For any given dose-response

relationship, a great variety of criteria or end points of toxicity could be used. The ideal criterion would be one closely associated with the molecular events resulting from exposure to the toxicant. It follows from this that a given chemical may have a family of dose-response relationships, 1 for each toxic end point. For example, a chemical that produces cancer through genotoxic effects, liver damage through inhibition of a specific enzyme, and CNS effects via a different mechanism, may have 3 distinct dose-response relationships, 1 for each end point. Early in the assessment of toxicity, little mechanistic information is usually available; thus, establishing a dose-response relationship based on the molecular mechanism of action is usually impossible. Indeed, it might not be approachable even for well-known toxicants. In the absence of a mechanistic molecular ideal criterion of toxicity, one looks to a measure of toxicity that is unequivocal and clearly relevant to the toxic effect. Such measures are often referred to as "effects-related biomarkers." For example, with a new compound chemically related to the class of organophosphorus insecticides, one might approach the measurement of toxicity by measuring the inhibition of cholinesterase in blood. In this way, one would be measuring, in a readily accessible system and using a technique that is convenient and reasonably precise, a prominent effect of the chemical and one that is usually pertinent to the mechanism by which toxicity is produced.

The selection of a toxic end point for measurement is not always so straightforward. Even the example cited above may be misleading, as an organophosphate may produce a decrease in blood cholinesterase, but this change may not be directly related to its toxicity. As additional data are gathered to suggest a mechanism of toxicity for any substance, other measures of toxicity may be selected. Although many end points are quantitative and precise, they are often indirect measures of toxicity. Changes in enzyme levels in blood can be indicative of tissue damage. For example, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are used to detect liver damage. Use of these enzymes in serum is yet another example of an effects-related biomarker because the change in enzyme activity in the blood is directly related to damage to liver cells. Much of clinical diagnostic medicine relies on effects-related biomarkers, but to be useful the relationship between the biomarker and the disease must be carefully established. Patterns of isoenzymes and their alteration may provide insight into the organ or system that is the site of toxic effects. As discussed later in this chapter, the new tools of toxicogenomics provide an unprecedented opportunity to discover new "effects-related biomarkers" in toxicology.

Many direct measures of effects are also not necessarily related to the mechanism by which a substance produces harm to an organism but have the advantage of permitting a causal relation to be drawn between the chemical and its action. For example, measurement of the alteration of the tone of smooth or skeletal muscle for substances acting on muscles represents a fundamental approach to toxicological assessment. Similarly, measures of heart rate, blood pressure, and electrical activity of heart muscle, nerve, and brain are examples of the use of physiological functions as indices of toxicity. Measurement can also take the form of a still higher level of integration, such as the degree of motor activity or behavioral change.

The measurements used as examples in the preceding discussion all assume prior information about the toxicant, such as its target organ or site of action or a fundamental effect. However, such information is usually available only after toxicological screening and testing based on other measures of toxicity. With a new substance, the customary starting point is a single dose acute toxicity test designed to provide preliminary identification of target organ



toxicity. Studies specifically designed with lethality as an end point are no longer recommended by the United States or international agencies. Data from acute studies provide essential information for choosing doses for repeated dosing studies as well as choosing specific toxicological end points for further study. Key elements of the study design must be a careful, disciplined, detailed observation of the intact animal extending from the time of administration of the toxicant to any clinical signs of distress, which may include detailed behavioral observations or physiological measures. It is recommended that these observations be taken over a 14-day period. From properly conducted observations, immensely informative data can be gathered by a trained toxicologist. Second, an acute toxicity study ordinarily is supported by histological examination of major tissues and organs for abnormalities. From these observations, one can usually obtain more specific information about the events leading to the various end points, the target organs involved, and often a suggestion about the possible mechanism of toxicity at a relatively fundamental level.

## Evaluating the Dose-Response Relationship

**Comparison of Dose Responses** Fig. 2-11 illustrates a hypothetical quantal dose-response curve for a desirable effect of a chemical (effective dose, ED) such as anesthesia, a toxic effect (toxic dose, ED) such as liver injury, and the lethal dose (LD). As depicted in Fig. 2-11, a parallelism is apparent between the ED curve and the curve depicting mortality (LD). It is tempting to view the parallel dose-response curves as indicative of identity of mechanism—that is, to conclude that the lethality is a simple extension of the therapeutic effect. Whereas this conclusion may ultimately prove to be correct in any particular case, it is not warranted solely on the basis of the 2 parallel lines. The same admonition applies to any pair of parallel “effect” curves or any other pair of toxicity or lethality curves.

**Therapeutic Index** The hypothetical curves in Fig. 2-11 illustrate 2 other interrelated points: the importance of the selection of the toxic criterion and the interpretation of comparative effect. The concept of the “therapeutic index” (TI), which was introduced by Paul Ehrlich in 1913, can be used to illustrate this relationship. Although the TI is directed toward a comparison of the therapeutically ED to the TD of a chemical, it is equally applicable to considerations of comparative toxicity. The TI in its broadest sense is defined as the ratio of the dose required to produce a toxic effect to

the dose needed to elicit the desired therapeutic response. Similarly, an index of comparative toxicity is obtained by the ratio of doses of 2 different materials to produce an identical response or the ratio of doses of the same material necessary to yield different toxic effects.

The most commonly used index of effect, whether beneficial or toxic, is the median effect dose ( $ED_{50}$ ). The TI of a drug is an approximate statement about the relative safety of a drug expressed as the ratio of the adverse end point or TD (historically the LD) to the therapeutic dose:

$$TI = \frac{TD_{50}}{ED_{50}}$$

From Fig. 2-11 one can approximate a TI by using these median doses. The larger the ratio, the greater is the relative safety. The  $ED_{50}$  is approximately 20, and the  $TD_{50}$  is about 60; thus, the TI is 3, a number indicating that reasonable care in exposure to the drug is necessary to avoid toxicity. However, the use of the median effective and median toxic doses is not without disadvantages, because median doses tell nothing about the slopes of the dose-response curves for therapeutic and toxic effects.

**Margins of Safety and Exposure** One way to overcome this deficiency is to use the  $ED_{99}$  for the desired effect and the  $TD_1$  for the undesired effect. These parameters are used in the calculation of the margin of safety (MOS):

$$MOS = \frac{TD_1}{ED_{99}}$$

The quantitative comparisons described above have been used mainly after a single administration of chemicals. However, for chemicals for which there is no beneficial or effective dose and exposures are likely to occur repeatedly, the ratio of  $TD_1$  to  $ED_{99}$  has little relevance. Thus, for nondrug chemicals, the term MOS has found use in risk assessment procedures as an indicator of the magnitude of the difference between an estimated “exposed dose” to a human population and the NOAEL or other benchmark dose determined in experimental animals.

A measure of the degree of accumulation of a chemical and/or its toxic effects can also be estimated from quantal toxicity data. The *chronicity index* of a chemical is a unitless value obtained by dividing its 1-dose  $TD_{50}$  by its 90-dose (90-day)  $TD_{50}$ , with both expressed in milligrams per kilogram per day. Theoretically, if no cumulative effect occurs over the doses, the chronicity index will be 1. If a compound were absolutely cumulative, the chronicity index would be 90.

Historically, statistical procedures similar to those used to calculate the  $LD_{50}$  can also be used to determine the lethal time 50 ( $LT_{50}$ ), or the time required for half the animals to die (Litchfield, 1949). The  $LT_{50}$  value for a chemical indicates the time course of the toxic effects but does not indicate whether 1 chemical is more toxic than another.

Frequently, dose-response curves from repeated-dose experimental animal studies (subacute, subchronic, or chronic) are used to estimate the NOAEL, or some other “benchmark” measure of minimal toxic response, such as the dose estimated to produce toxic effects in 10% of the population ( $TD_{10}$ ) (see also Chap. 4). These estimates of minimal TD, derived from quantal dose-response curves, can be used in risk assessment to derive a “margin of exposure” (MOE) index. This index compares the estimated daily exposure, in milligrams per kilogram per day, that might occur under a given set of circumstances with some estimated value from the quantal dose-response relationship (eg, NOAEL or  $TD_{10}$ ). Like the

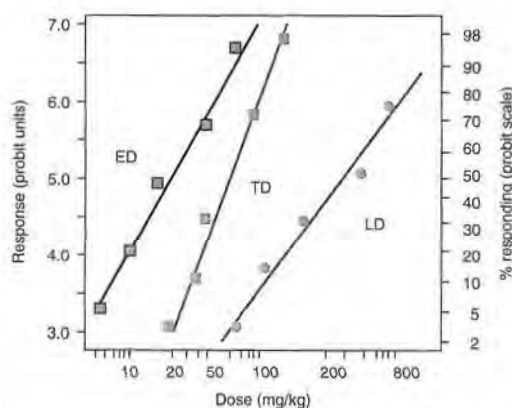


Figure 2-11. Comparison of effective dose (ED), toxic dose (TD), and lethal dose (LD). The plot is of log dosage versus percentage of population responding in probit units.



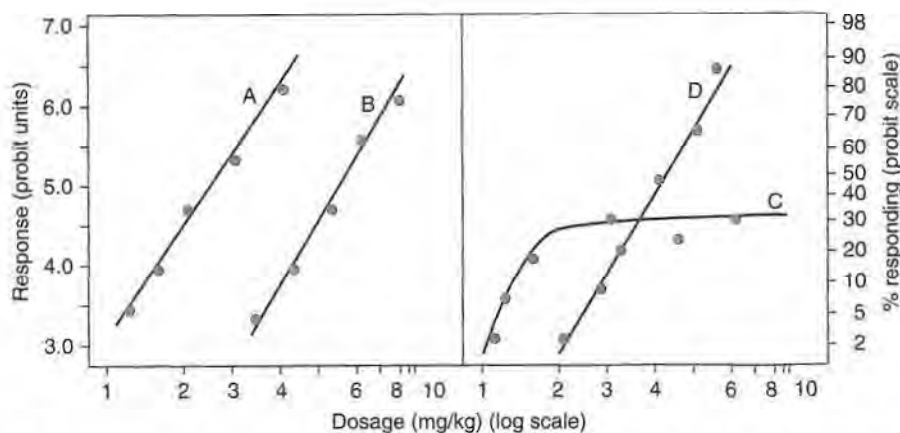


Figure 2-12. Schematic representation of the difference in the dose-response curves for 4 chemicals (A-D), illustrating the difference between potency and efficacy (see text).

MOS, the MOE is often expressed as a ratio of these 2 values. Thus, for example, if an estimate of human exposure to a pesticide residue yielded a value of 0.001 mg/kg per day, and a  $TD_{10}$  of 1 mg/kg per day was determined for that same pesticide, the MOE would be 1000. This value indicates that the estimate of daily exposure under the described set of conditions is 1/1000 the estimated daily dose that would cause evident toxicity in 10% of exposed animals. (See Chap. 4 for a more complete discussion of benchmark doses, NOAELs, and MOE.)

**Potency versus Efficacy** To compare the toxic effects of 2 or more chemicals, the dose response to the toxic effects of each chemical must be established. One can then compare the potency and maximal efficacy of the 2 chemicals to produce a toxic effect. These 2 important terms can be explained by reference to Fig. 2-12, which depicts dose-response curves to 4 different chemicals for the frequency of a particular toxic effect, such as the production of tumors. Chemical A is said to be more potent than chemical B because of their relative positions along the dosage axis. Potency thus refers to the range of doses over which a chemical produces increasing responses. Thus, A is more potent than B and C is more potent than D. Maximal efficacy reflects the limit of the dose-response relationship on the response axis to a certain chemical. Chemicals A and B have equal maximal efficacy, whereas the maximal efficacy of C is less than that of D.

## VARIATION IN TOXIC RESPONSES

### Selective Toxicity

*Selective toxicity* means that a chemical produces injury to 1 kind of living matter without harming another form of life even though the 2 may exist in intimate contact (Albert, 1973). The living matter that is injured is termed the *uneconomic form* (or undesirable), and the matter protected is called the *economic form* (or desirable). They may be related to each other as parasite and host or may be 2 tissues in 1 organism. This biological diversity interferes with the ability of ecotoxicologists to predict the toxic effects of a chemical in 1 species (humans) from experiments performed in another species (laboratory animals). However, by taking advantage of the biological diversity, it is possible to develop chemicals that are lethal for an undesired species and harmless for other species. In agriculture, for example, there are fungi, insects, and even competitive plants that injure the crop, and thus selective pesticides are needed. Similarly, animal husbandry and human medicine require

chemicals, such as antibiotics, that are selectively toxic to the undesirable form but do not produce damage to the desirable form.

Drugs and other chemicals used for selective toxic purposes are selective for 1 of 2 reasons. Either (1) the chemical is equally toxic to both economic and uneconomic cells but is accumulated mainly by uneconomic cells or (2) it reacts fairly specifically with a cytological or a biochemical feature that is absent from or does not play an important role in the economic form (Albert, 1973). Selectivity resulting from differences in distribution usually is caused by differences in the absorption, biotransformation, or excretion of the toxicant. The selective toxicity of an insecticide spray may be partly due to a larger surface area per unit weight that causes the insect to absorb a proportionally larger dose than does the mammal being sprayed. The effectiveness of radioactive iodine in the treatment of hyperthyroidism (as well as its thyroid carcinogenicity) is due to the selective ability of the thyroid gland to accumulate iodine. A major reason why chemicals are toxic to one, but not to another, type of tissue is that there are differences in accumulation of the ultimate toxic compound in various tissues. This, in turn, may be due to differences in the ability of various tissues to transport or biotransform the chemical into the ultimate toxic product.

Selective toxicity caused by differences in comparative cytology is exemplified by a comparison of plant and animal cells. Plants differ from animals in many ways—for example, absence of a nervous system, an efficient circulatory system, and muscles as well as the presence of a photosynthetic mechanism and cell walls. The fact that bacteria contain cell walls and humans do not has been utilized in developing selective toxic chemotherapeutic agents, such as penicillin and cephalosporins, that kill bacteria but are relatively nontoxic to mammalian cells.

Selective toxicity can also be a result of a difference in biochemistry in the 2 types of cells. For example, bacteria do not absorb folic acid but synthesize it from *p*-aminobenzoic acid, glutamic acid, and pteridine, whereas mammals cannot synthesize folic acid but have to absorb it from the diet. Thus, sulfonamide drugs are selectively toxic to bacteria because the sulfonamides, which resemble *p*-aminobenzoic acid in both charge and dimensions, antagonize the incorporation of *p*-aminobenzoic acid into the folic acid molecule—a reaction that humans do not carry out.

### Species Differences

Although a basic tenet of toxicology is that “experimental results in animals, when properly qualified, are applicable to humans,” it is important to recognize that both quantitative and qualitative



differences in response to toxic substances may occur among different species. As discussed above, there are many reasons for selective toxicity among different species. Even among phylogenetically similar species (eg, rats, mice, guinea pigs, and hamsters), large differences in response may occur. For example, the  $LD_{50}$  for the highly toxic dioxin, TCDD, differs by more than 1000-fold between guinea pigs and hamsters. Not only the lethal dose for TCDD but also the particular target organs affected vary widely among species. Species differences in response to carcinogenic chemicals represent an important issue in regulatory risk assessment. As discussed in Chap. 4, extrapolation of laboratory animal data to infer human cancer risk is currently a key component of regulatory decision making. The validity of this approach of course depends on the relevance of the experimental animal model to humans. Large differences in carcinogenic response between experimental animal species are not unusual. For example, mice are highly resistant to the hepatocarcinogenic effects of the fungal toxin AFB<sub>1</sub>. Dietary doses as high as 10,000 ppb failed to produce liver cancer in mice, whereas in rats dietary doses as low as 15 ppb produced a significant increase in liver tumors (Wogan *et al.*, 1974). The mechanistic basis for this dramatic difference in response appears to be entirely related to species differences in the expression of a particular form of glutathione *S*-transferase (mGSTA3-3) that has unusually high catalytic activity toward the carcinogenic epoxide of aflatoxin (Eaton and Gallagher, 1994). Mice express this enzyme constitutively, whereas rats normally express a closely related form with much less detoxifying activity toward aflatoxin epoxide. Interestingly, rats do possess the gene for a form of glutathione *S*-transferase with high catalytic activity toward aflatoxin epoxide (rGSTA5-5) that is inducible by certain dietary antioxidants and drugs. Thus, dietary treatment can dramatically change the sensitivity of a species to a carcinogen.

Other examples in which large species differences in response to carcinogens have been observed include the development of renal tumors from 2,3,5-trimethylpentane and  $\alpha$ -limonene in male rats (Lehman-McKeeman and Caudill, 1992), the production of liver tumors from "peroxisomal proliferators" such as the antilipidemic drug clofibrate and the common solvent trichloroethylene (Roberts, 1999), and the induction of nasal carcinomas in rats after inhalation exposure to formaldehyde (Monticello and Morgan, 1997).

Identifying the mechanistic basis for species differences in response to chemicals is an important part of toxicology because only through a thorough understanding of these differences can the relevance of animal data to human response be verified.

## Individual Differences in Response

Even within a species, large interindividual differences in response to a chemical can occur because of subtle genetic differences. Hereditary differences in a single gene that occur in more than 1% of the population are referred to as *genetic polymorphism* and may be responsible for idiosyncratic reactions to chemicals, as discussed earlier in this chapter. However, genetic polymorphism may have other important but less dramatic effects than those described for acute idiosyncratic responses (such as that occurring in pseudocholinesterase-deficient individuals after succinylcholine exposure). For example, it is recognized that approximately 50% of the Caucasian population has a gene deletion for the enzyme glutathione *S*-transferase M1. This enzyme has no apparent significant physiological function, and thus homozygotes for the gene deletion (eg, those who lack both copies of the normal gene) are functionally and physiologically normal. However, epidemiological studies have indicated that smokers who are homozygous for the null

allele may be at slightly increased risk of developing lung cancer compared with smokers who have 1 or both copies of the normal gene (Mohr *et al.*, 2003). Chap. 6 provides additional examples of genetic differences in biotransformation enzymes that may be important determinants of variability in individual susceptibility to chemical exposures.

Genetic polymorphism in physiologically important genes may also be responsible for interindividual differences in toxic responses. For example, studies in transgenic mice have shown that mice possessing 1 copy of a mutated *p53* gene (a so-called tumor suppressor gene; see Chap. 8) are much more susceptible to some chemical carcinogens than are mice with 2 normal copies of the gene (Tennant *et al.*, 1999). In humans, there is evidence that possessing 1 mutated copy of a tumor suppressor gene greatly increases the risk of developing certain cancers. For example, retinoblastoma is a largely inherited form of cancer that arises because of the presence of 2 copies of a defective tumor suppressor gene (the Rb gene) (Wiman, 1993). Individuals with 1 mutated copy of the Rb gene and 1 normal copy are not destined to acquire the disease (as are those with 2 copies of the mutated gene), although their chance of acquiring it is much greater than that of persons with 2 normal Rb genes. This is the case because both copies of the gene must be nonfunctional for the disease to develop. With 1 mutated copy present genetically, the probability of acquiring a mutation of the second gene (potentially from exposure to environmental mutagens) is much greater than the probability of acquiring independent mutations in both copies of the gene as would be necessary in people with 2 normal Rb alleles. (See Chap. 8 for additional discussion of tumor suppressor genes.)

As our understanding of the human genome increases, more "susceptibility" genes will be discovered, and it is likely that the etiology of many chronic diseases will be shown to be related to a combination of genetics and environment. Simple blood tests may ultimately be developed that allow an individual to learn whether he or she may be particularly susceptible to specific drugs or environmental pollutants. Although the public health significance of this type of information could be immense, the disclosure of such information raises many important ethical and legal issues that must be addressed before wide use of such tests.

The study of "gene-environment" interactions, or "ecogenetics" (Costa and Eaton, 2006), is a rapidly developing field of substantial relevance to toxicology. It is likely that the majority of chronic diseases develop as a result of the complex interplay between multiple genes and the myriad of environmental factors, including diet, lifestyle, and occupational and/or environmental exposures to toxic substances. The growing field of epigenetics, discussed in more detail later in this chapter, is likely to have an equally great impact on the science of toxicology, as it is likely that many xenobiotics will be found to exert many of their chronic adverse effects through subtle effects on gene expression.

## DESCRIPTIVE ANIMAL TOXICITY TESTS

Two main principles underlie all descriptive animal toxicity testing. The first is that the effects produced by a compound in laboratory animals, when properly qualified, are applicable to humans. This premise applies to all of experimental biology and medicine. Most, if not all, known chemical carcinogens in humans are carcinogenic in some species, but not necessarily in all species of laboratory animals. It has become increasingly evident that the converse—that all chemicals identified as carcinogenic in laboratory animals are also carcinogenic in humans—is not true (Dybing and Sanner, 1999; Grisham, 1997; Hengstler *et al.*, 1999). However, for regulatory



and risk assessment purposes, positive carcinogenicity tests in animals are usually interpreted as indicative of potential human carcinogenicity. If a clear understanding of the mechanism of action of the carcinogen indicates that a positive response in animals is not relevant to humans, a positive animal bioassay may be considered irrelevant for human risk assessment (see Chap. 4). This species variation in carcinogenic response appears to be due in many instances to differences in biotransformation of the procarcinogen to the ultimate carcinogen (see Chap. 6).

The second principle is that exposure of experimental animals to chemicals in high doses is a necessary and valid method of discovering possible hazards in humans. This principle is based on the quantal dose-response concept that the incidence of an effect in a population is greater as the dose or exposure increases. Practical considerations in the design of experimental model systems require that the number of animals used in toxicology experiments always be small compared with the size of human populations at risk. Obtaining statistically valid results from such small groups of animals requires the use of relatively large doses so that the effect will occur frequently enough to be detected. However, the use of high doses can create problems in interpretation if the response(s) obtained at high doses does not occur at low doses. Thus, for example, it has been shown that bladder tumors observed in rats fed very high doses of saccharin will not occur at the much lower doses of saccharin encountered in the human diet. At the high concentrations fed to rats, saccharin forms an insoluble precipitate in the bladder that subsequently results in chronic irritation of bladder epithelium, enhanced cell proliferation, and ultimately bladder tumors (Cohen, 1998, 1999). In vitro studies have shown that precipitation of saccharin in human urine will not occur at the concentrations

that could be obtained from even extraordinary consumption of this artificial sweetener. As noted above and shown in Fig. 2-8, even for mutagenic chemicals that form DNA adducts, the response at high doses, as seen for DBC, may not be linear at low doses, although for another DNA-reactive carcinogen, AFB<sub>1</sub>, the high-dose data were reflective of low-dose response in an approximately linear fashion. Examples such as these illustrate the importance of considering the molecular, biochemical, and cellular mechanisms responsible for toxicological responses when extrapolating from high to low dose and across species.

Toxicity tests are not designed to demonstrate that a chemical is safe but to characterize the toxic effects a chemical can produce. Although there are no set toxicology tests that have to be performed on every chemical intended for commerce, a tiered approach typical of many hazard assessment programs is illustrated in Fig. 2-13. Depending on the eventual use of the chemical, the toxic effects produced by structural analogs of the chemical, as well as the toxic effects produced by the chemical itself, contribute to the determination of the toxicology tests that should be performed. The FDA, EPA, and Organization for Economic Cooperation and Development (OECD) have written good laboratory practice (GLP) standards and other guidance that stipulate that procedure must be defined and accountability documented. These guidelines are expected to be followed when toxicity tests are conducted in support of the introduction of a chemical to the market.

The following sections provide an overview of basic toxicity testing procedures in use today. For a detailed description of these tests, the reader is referred to several authoritative texts on this subject (Barile, 2010; Hayes, 2008; Jacobson-Kram and Keller, 2006; Eaton and Gallagher, 2010).

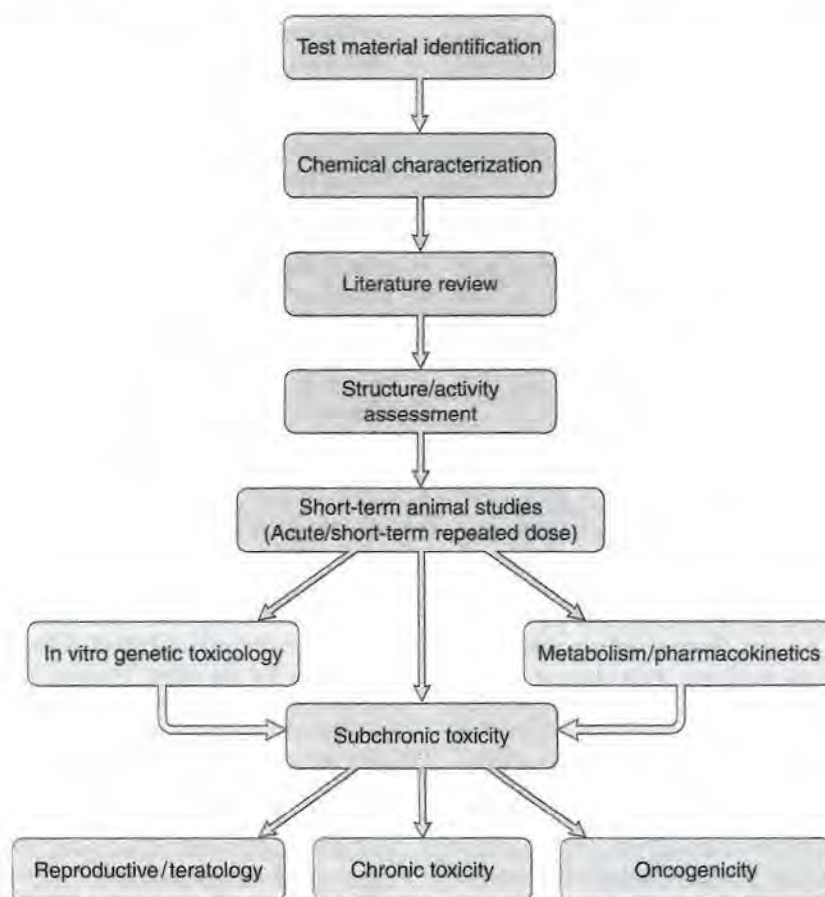


Figure 2-13. Typical tiered testing scheme for the toxicological evaluation of new chemicals. (From Wilson *et al.* 2008, Fig. 19-1, p. 918.)



Table 2-3

## International Conference on Harmonization (ICH) Codification of "Safety" Protocols

## Carcinogenicity studies

S1A	Need for Carcinogenicity Studies of Pharmaceuticals
S1B	Testing for Carcinogenicity of Pharmaceuticals
S1C(R1)	Dose Selection for Carcinogenicity Studies of Pharmaceuticals & Limit Dose

## Genotoxicity studies

S2A	Guidance on Specific Aspects of Regulatory Genotoxicity Tests for Pharmaceuticals
S2B	Genotoxicity: A Standard Battery for Genotoxicity Testing of Pharmaceuticals

## Toxicokinetics and pharmacokinetics

S3A	Note for Guidance on Toxicokinetics: The Assessment of Systemic Exposure in Toxicity Studies
S3B	Pharmacokinetics: Guidance for Repeated Dose Tissue Distribution Studies

## Toxicity testing

	Single Dose Toxicity Tests
S4	Duration of Chronic Toxicity Testing in Animals (Rodent and Non Rodent Toxicity Testing)

## Reproductive toxicology

S5(R2)	Detection of Toxicity to Reproduction for Medicinal Products & Toxicity to Male Fertility
--------	---

## Biotechnological products

S6	Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals
----	--

## Pharmacology studies

S7A	Safety Pharmacology Studies for Human Pharmaceuticals
S7B	The Non-Clinical Evaluation of the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals

## Immunotoxicology studies

S8	Immunotoxicity Studies for Human Pharmaceuticals
----	--

## Joint safety/efficacy (multidisciplinary) topic

M3(R1)	Non-Clinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals
--------	--

*Titles and abbreviations adopted in November 2005. Data from [http://www.ich.org/fileadmin/Public\\_Web\\_Site/ICH\\_Products/Guidelines/Guidelines\\_Index.pdf](http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Guidelines_Index.pdf).*

Although different countries have often had different testing requirements for toxicity testing/product safety evaluation, efforts to "harmonize" such testing protocols have resulted in more standardized approaches. The International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use includes regulatory authorities from Europe, Japan, and the United States (primarily the FDA), as well as experts from the pharmaceutical industry in the 3 regions, who worked together to develop internationally recognized scientific and technical approaches to pharmaceutical product registration. ICH has adopted guidelines for most areas of toxicity testing (Table 2-3). In addition to safety assessment (ICH guidelines designated with an "S"), ICH has also established guidelines on quality (Q), efficacy (E), and multidisciplinary (M) topics. (See <http://www.ich.org/products/guidelines.htm>) for a description of current ICH guidelines and reviews by Pugsley *et al.* (2008, 2011) for a detailed discussion of *in vitro* and *in vivo* approaches to safety pharmacology that has been informed by the ICH regulatory guidance document for preclinical safety testing of drugs.)

Typically, a tiered approach is used, with subsequent tests dependent on results of initial studies. A general framework for how new chemicals are evaluated for toxicity is shown in Fig 2-13. Early studies require careful chemical evaluation of the compound

or mixture to assess purity, stability, solubility, and other physicochemical factors that could impact the ability of the test compound to be delivered effectively to animals. Once this information is obtained, the chemical structure of the test compound is compared with similar chemicals for which toxicological information is already available. Structure-activity relationships may be derived from a review of existing toxicological literature, and can provide additional guidance on design of acute and repeated-dose experiments, and what specialized tests need to be completed. Once such basic information has been compiled and evaluated, the test compound is then administered to animals in acute and repeated-dose studies.

Because of increased societal pressure to reduce or eliminate the use of animals in toxicity testing, while also ensuring that new chemicals do not represent unreasonable risks to human health or the environment, regulatory agencies have been encouraging new approaches to descriptive toxicity tests that do not rely on laboratory animals. For example, the European Union (EU) promulgated an important regulatory initiative for the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH). The implementation of REACH "will have significant impact on applied toxicology and exposure assessment by stimulating innovation in sampling and analysis, toxicology testing, exposure modeling, alternative toxicity testing, and risk assessment practices."



(Williams *et al.*, 2009b). Alternative, *in vitro* approaches to toxicity assessment are likely to transform the way that product safety evaluation is done in the future, although the standard approaches to hazard evaluation described in this section are likely to continue as the mainstay of toxicity evaluation for the next decade, irrespective of the fact that some areas, such as acute toxicity testing and eye irritation, are likely to be largely replaced by *in vitro* tests in the next decade (Ukelis *et al.*, 2008).

The development of new “omics” technologies (discussed later in this section) may have profound implications for toxicity testing in the future (NAS/NRC, 2007). The recognition that many of the existing chemicals in commercial use today, as well as new chemicals being introduced into commerce, have little toxicological information about them has prompted calls for new “high-throughput” approaches to toxicity testing that will allow at least basic hazard characterization for the thousands of untested chemicals currently in the marketplace, as well as the many new chemicals that are introduced each year. A report from the National Academy of Sciences/National Research Council in 2007 called for a “paradigm shift” in how toxicity testing is done (NAS/NRC, 2007). A key component of this new vision on toxicity testing is the use of an extensive battery of *in vitro* tests to evaluate “pathways” of toxicity (NAS/NRC, 2010). The hope is that new technologies in genomics, transcriptomics, proteomics, metabolomics, and bioinformatics (discussed later in this chapter) can be combined with automated high-throughput technologies to create a tiered structure for toxicity testing. The approach to using biochemical and molecular pathway-based analyses, rather than apical end points (eg, target organ damage, mutagenesis, carcinogenesis, reproductive and developmental effects), to identify potentially problematic chemicals early in their development is particularly attractive from a time frame and economic perspective (NAS/NRC, 2010). However, it is also recognized that validation of such tests is critically important to the reliable use of such screening technologies, and that the traditional *in vivo* studies described in the following section will continue to serve an important role in hazard evaluations for years to come, especially as a means of validating new high-throughput screening approaches.

## Acute Toxicity Testing

Generally, the first toxicity test performed on a new chemical is acute toxicity, determined from the administration of a single exposure. The objectives of acute toxicity testing are to: (1) provide an estimate of the intrinsic toxicity of the substance, often times expressed as an approximate LD (eg, LD<sub>50</sub>), (2) provide information on target organs and other clinical manifestations of toxicity, (3) identify species differences and susceptible species, (4) establish the reversibility of the toxic response, and (5) provide information that will assist in the design and dose selection for longer-term (subchronic, chronic) studies. It should be noted that the ICH recommended in 1991 (D’Arcy and Harron, 1992) the elimination of LD<sub>50</sub> determinations for pharmaceuticals, although other regulatory requirements, for example, pesticide registration, may still require determinations of LD<sub>50</sub>s.

The LD<sub>50</sub> and other acute toxic effects are determined after 1 or more routes of administration (1 route being oral or the intended route of exposure) in 1 or more species. The species most often used are the mouse and rat. Studies are performed in both adult male and female animals. Food is often withheld the night before dosing. The number of animals that die in a 14-day period after a single dosage is tabulated. In addition to mortality and weight, daily examination of test animals should be conducted for signs

of intoxication, lethargy, behavioral modifications, morbidity, food consumption, and so on.

Determination of the LD<sub>50</sub> has become a public issue because of increasing concern for the welfare and protection of laboratory animals. The LD<sub>50</sub> is not a biological constant. Many factors influence toxicity and thus may alter the estimation of the LD<sub>50</sub> in any particular study. Factors such as animal strain, age, and weight, type of feed, caging, pretrial fasting time, method of administration, volume and type of suspension medium, and duration of observation have all been shown to influence adverse responses to toxic substances. These and other factors have been discussed in detail in earlier editions of this textbook (Doull, 1980). Because of this inherent variability in LD<sub>50</sub> estimates, it is now recognized that for most purposes it is only necessary to characterize the LD<sub>50</sub> within an order of magnitude range such as 5 to 50 mg/kg, 50 to 500 mg/kg, and so on.

There are several traditional approaches to determining the LD<sub>50</sub> and its 95% confidence limit as well as the slope of the probit line. The reader is referred to the classic works of Litchfield and Wilcoxon (1949), Bliss (1957), and Finney (1971) for a description of the mechanics of these procedures. Other statistical techniques that require fewer animals, such as the “moving averages” method of Thompson and Weill (Weil, 1952), are available but do not provide confidence limits for the LD<sub>50</sub> and the slope of the probit line. Finney (1985) has succinctly summarized the advantages and deficiencies of many of the traditional methods. For most circumstances, an adequate estimate of the LD<sub>50</sub> and an approximation of the 95% confidence intervals can be obtained with as few as 6 to 9 animals, using the “up-and-down” method as modified by Bruce (1985). When this method was compared with traditional methods that typically utilize 40 to 50 animals, excellent agreement was obtained for all 10 compounds tested (Bruce, 1987). In mice and rats the LD<sub>50</sub> is usually determined as described above, but in the larger species only an approximation of the LD<sub>50</sub> is obtained by increasing the dose in the same animal until serious toxic effects are evident.

Alternative *in vitro* approaches to estimating the LD<sub>50</sub> have been proposed. For example, the *Registry of Cytotoxicity* (RC), originally published in German in 1998 (Halle, 2003), was developed by linear regression analysis of the mean IC<sub>50</sub> values determined in mammalian cells in culture and the LD<sub>50</sub> values reported in the literature from various laboratory species. Using this approach, the authors predicted (within a reasonable dose range) the acute oral LD<sub>50</sub> for 252 of 347 xenobiotics, and the intravenous LD<sub>50</sub> for rats and/or mice for 117 of 150 xenobiotics (Halle, 2003). Of course, such *in vitro* approaches do not fully account for dispositional effects that could result in large species differences in acute toxicity, but do provide a rapid first approximation of acute toxicity without the use of experimental animals.

If there is a reasonable likelihood of substantial exposure to the material by dermal or inhalation exposure, acute dermal and acute inhalation studies are performed. When animals are exposed acutely to chemicals in the air they breathe or the water they (fish) live in, the dose the animals receive is usually not known. For these situations, the lethal concentration 50 (LC<sub>50</sub>) is usually determined, that is, the concentration of chemical in the air or water that causes death to 50% of the animals. In reporting an LC<sub>50</sub>, it is imperative that the time of exposure be indicated. The acute dermal toxicity test is usually performed in rabbits. The site of application is shaved. The test substance is kept in contact with the skin for 24 hours by wrapping the skin with an impervious plastic material. At the end of the exposure period, the wrapping is removed and the skin is wiped to remove any test substance still remaining. Animals are observed at various intervals for 14 days, and the LD<sub>50</sub> is calculated. If no



toxicity is evident at 2 g/kg, further acute dermal toxicity testing is usually not performed. Acute inhalation studies are performed that are similar to other acute toxicity studies except that the route of exposure is inhalation. Most often, the length of exposure is 4 hours.

By themselves LD<sub>50</sub> and LC<sub>50</sub> values are of limited significance given the growing sophistication of target organ toxicity end points and mechanistic analysis. The most meaningful scientific information derived from acute toxicity tests comes from clinical observations and post-mortem examination of animals rather than from the specific LD<sub>50</sub> value.

## Skin and Eye Irritations

The ability of a chemical to irritate the skin and eye after an acute exposure is usually determined in rabbits. For the dermal irritation test (Draize test), rabbits are prepared by removal of fur on a section of the back by electric clippers. The chemical is applied to the skin (0.5 mL of liquid or 0.5 g of solid) under 4 covered gauze patches (1 in square; 1 intact and 2 abraded skin sites on each animal) and usually kept in contact for 4 hours. The nature of the covering patches depends on whether occlusive, semioclusive, or nonocclusive tests are desired. For occlusive testing, the test material is covered with an impervious plastic sheet; for semioclusive tests, a gauze dressing may be used. Occasionally, studies may require that the material be applied to abraded skin. The degree of skin irritation is scored for erythema (redness), eschar (scab), and edema (swelling) formation, and corrosive action. These dermal irritation observations are repeated at various intervals after the covered patch has been removed. To determine the degree of ocular irritation, the chemical is instilled into 1 eye (0.1 mL of liquid or 100 mg of solid) of each test rabbit. The contralateral eye is used as the control. The eyes of the rabbits are then examined at various times after application.

Controversy over this test has led to the development of alternative in vitro models for evaluating cutaneous and ocular toxicity of substances. The various in vitro methods that have been evaluated for this purpose include epidermal keratinocyte and corneal epithelial cell culture models. Several commercially available "reconstructed human epidermis" models have been developed explicitly for the purposes of in vitro skin irritation and corrosion tests (Netzlaff *et al.*, 2005).

## Sensitization

Information about the potential of a chemical to sensitize skin is needed in addition to irritation testing for all materials that may repeatedly come into contact with the skin. Numerous procedures have been developed to determine the potential of substances to induce a sensitization reaction in humans (delayed hypersensitivity reaction), including the Draize test, the open epicutaneous test, the Buehler test, Freund's complete adjuvant test, the optimization test, the split adjuvant test, and the guinea pig maximization test (Hayes *et al.*, 2008; Rush *et al.*, 1995). Although they differ in regard to route and frequency of duration, they all utilize the guinea pig as the preferred test species. In general, the test chemical is administered to the shaved skin topically, intradermally, or both and may include the use of adjuvant to enhance the sensitivity of the assay. Multiple administrations of the test substance are generally given over a period of 2 to 4 weeks. Depending on the specific protocol, the treated area may be occluded. Approximately 2 to 3 weeks after the last treatment, the animals are challenged with a nonirritating concentration of the test substance and the development of erythema is evaluated.

## Subacute (Repeated-Dose Study)

Subacute toxicity tests are performed to obtain information on the toxicity of a chemical after repeated administration and as an aid to establish doses for subchronic studies. A typical protocol is to give 3 to 4 different dosages of the chemicals to the animals by mixing it in their feed. For rats, 10 animals per sex per dose are often used; for dogs, 3 dosages and 3 to 4 animals per sex are used. Clinical chemistry and histopathology are performed after either 14 or 28 days of exposure, as described in the section "Subchronic."

## Subchronic

The toxicity of a chemical after subchronic exposure is then determined. Subchronic exposure can last for different periods of time, but 90 days is the most common test duration. The principal goals of the subchronic study are to establish a NOAEL and to further identify and characterize the specific organ or organs affected by the test compound after repeated administration. One may also obtain a "lowest observed adverse effect level" (LOAEL) as well as the NOAEL for the species tested. The numbers obtained for NOAEL and LOAEL will depend on how closely the dosages are spaced and the number of animals examined. Determinations of NOAELs and LOAELs have numerous regulatory implications. For example, the EPA utilizes the NOAEL to calculate the *reference dose* (RfD), which may be used to establish regulatory values for "acceptable" pollutant levels (Barnes and Dourson, 1988) (see Chap. 4). An alternative to the NOAEL approach referred to as the *benchmark dose* uses all the experimental data to fit 1 or more dose-response curves (Crump, 1984). These curves are then used to estimate a benchmark dose that is defined as "the statistical lower bound on a dose corresponding to a specified level of risk" (Allen *et al.*, 1994a). Although subchronic studies are frequently the primary or sole source of experimental data to determine both the NOAEL and the benchmark dose, these concepts can be applied to other types of toxicity testing protocols, such as that for chronic toxicity or developmental toxicity (Allen *et al.*, 1994a,b; Faustman *et al.*, 1994) (see also Chap. 4 for a complete discussion of the derivation and use of NOAELs, RfDs, and benchmark doses). If chronic studies have been completed, these data are generally used for NOAEL and LOAEL estimates in preference to data from subchronic studies.

A subchronic study is usually conducted in 2 species (usually rat and dog for FDA, and mouse for EPA) by the route of intended exposure (usually oral). At least 3 doses are employed (a high dose that produces toxicity but does not cause more than 10% fatalities, a low dose that produces no apparent toxic effects, and an intermediate dose) with 10 to 20 rodents and 4 to 6 dogs of each sex per dose. Each animal should be uniquely identified with permanent markings such as ear tags, tattoos, or electronically coded microchip implants. Only healthy animals should be used, and each animal should be housed individually in an adequately controlled environment. When the test compound is administered in the diet over a prolonged period of time (subchronic and chronic studies), the concentration in the diet should be adjusted periodically (weekly for the first 12–14 weeks) to maintain a constant intake of material based on food consumption and rate of change in body weight (Wilson *et al.*, 2008). Animals should be observed once or twice daily for signs of toxicity, including changes in body weight, diet consumption, changes in fur color or texture, respiratory or cardiovascular distress, motor and behavioral abnormalities, and palpable masses. All premature deaths should be recorded and necropsied as soon as possible. Severely moribund animals should be terminated immediately to preserve tissues and reduce unnecessary suffering.



At the end of the 90-day study, all the remaining animals should be terminated and blood and tissues should be collected for further analysis. The gross and microscopic condition of the organs and tissues (about 15–20) and the weight of the major organs (about 12) are recorded and evaluated. Hematology and blood chemistry measurements are usually done before, in the middle of, and at the termination of exposure. Hematology measurements usually include hemoglobin concentration, hematocrit, erythrocyte counts, total and differential leukocyte counts, platelet count, clotting time, and prothrombin time. Clinical chemistry determinations commonly made include glucose, calcium, potassium, urea nitrogen, ALT, serum AST, gamma-glutamyltranspeptidase (GGT), sorbitol dehydrogenase, lactic dehydrogenase, alkaline phosphatase, creatinine, bilirubin, triglycerides, cholesterol, albumin, globulin, and total protein. Urinalysis is usually performed in the middle of and at the termination of the testing period and often includes determination of specific gravity or osmolality, pH, proteins, glucose, ketones, bilirubin, and urobilinogen as well as microscopic examination of formed elements. If humans are likely to have significant exposure to the chemical by dermal contact or inhalation, subchronic dermal and/or inhalation experiments may also be required. Subchronic toxicity studies not only characterize the dose–response relationship of a test substance after repeated administration but also provide data for a more reasonable prediction of appropriate doses for chronic exposure studies.

For chemicals that are to be registered as drugs, acute and subchronic studies (and potentially additional special tests if a chemical has unusual toxic effects or therapeutic purposes) must be completed before the company can file an Investigational New Drug (IND) application with the FDA. If the application is approved, clinical trials can commence. At the same time phase I, phase II, and phase III clinical trials are performed, chronic exposure of the animals to the test compound can be carried out in laboratory animals, along with additional specialized tests.

## Chronic

Long-term or chronic exposure studies are performed similarly to subchronic studies except that the period of exposure is longer than 3 months. In rodents, chronic exposures are usually for 6 months to 2 years. Chronic studies in nonrodent species are usually for 1 year but may be longer. The length of exposure is somewhat dependent on the intended period of exposure in humans. For example, for pharmaceuticals, the ICH S4 guidance calls for studies of 6 months in duration in rodents, and 9 months in nonrodents. However, if the chemical is a food additive with the potential for lifetime exposure in humans, a chronic study up to 2 years in duration is likely to be required.

Dose selection is critical in these studies to ensure that premature mortality from chronic toxicity does not limit the number of animals that survive to a normal life expectancy. Most regulatory guidelines require that the highest dose administered be the estimated maximum tolerable dose (MTD, also commonly referred to as the “minimally toxic dose”). This is generally derived from subchronic studies, but additional longer studies (eg, 6 months) may be necessary if delayed effects or extensive cumulative toxicity are indicated in the 90-day subchronic study. The MTD has had various definitions (Haseman, 1985). It has been defined by some regulatory agencies as the dose that suppresses body weight gain slightly (ie, 10%) in a 90-day subchronic study (Reno, 1997). However, regulatory agencies may also consider the use of parameters other than weight gain, such as physiological and pharmacokinetic considerations and urinary metabolite profiles, as indicators

of an appropriate MTD (Reno, 1997). Generally, 1 or 2 additional doses, usually fractions of the MTD (eg, one-half and one-quarter MTD), and a control group are tested.

Chronic toxicity tests may include a consideration of the carcinogenic potential of chemicals so that a separate lifetime feeding study that addresses carcinogenicity does not have to be performed. However, specific chronic studies designed to assess the carcinogenic potential of a substance may be required (see below).

## Developmental and Reproductive Toxicity

The effects of chemicals on reproduction and development also need to be determined. *Developmental toxicology* is the study of adverse effects on the developing organism occurring anytime during the life span of the organism that may result from exposure to chemical or physical agents before conception (either parent), during prenatal development, or postnatally until the time of puberty. *Teratology* is the study of defects induced during development between conception and birth (see Chap. 10). *Reproductive toxicology* is the study of the occurrence of adverse effects on the male or female reproductive system that may result from exposure to chemical or physical agents (see Chap. 20).

Several types of animal tests are utilized to examine the potential of an agent to alter development and reproduction. (For a detailed description of reproductive and developmental toxicity testing procedures, see Christian [2008].) General fertility and reproductive performance (segment I) tests are usually performed in rats with 2 or 3 doses (20 rats per sex per dose) of the test chemical (neither produces maternal toxicity). Males are given the chemical 60 days and females 14 days before mating. The animals are given the chemical throughout gestation and lactation. Typical observations made include the percentage of females that become pregnant, the number of stillborn and live offspring, and the weight, growth, survival, and general condition of the offspring during the first 3 weeks of life.

The potential of chemicals to disrupt normal embryonic and/or fetal development (teratogenic effects) is also determined in laboratory animals. Current guidelines for these segment II studies call for the use of 2 species, including 1 nonrodent species (usually rabbits). Teratogens are most effective when administered during the first trimester, the period of organogenesis. Thus, the animals (usually 12 rabbits and 24 rats or mice per group) are usually exposed to 1 of 3 dosages during organogenesis (days 7–17 in rodents and 7–19 in rabbits), and the fetuses are removed by cesarean section a day before the estimated time of delivery (gestational days 29 for rabbit, 20 for rat, and 18 for mouse). The uterus is excised and weighed and then examined for the number of live, dead, and resorbed fetuses. Live fetuses are weighed; half of each litter is examined for skeletal abnormalities and the remaining half for soft tissue anomalies.

The perinatal and postnatal toxicities of chemicals also are often examined (segment III). This test is performed by administering the test compound to rats from the 15th day of gestation throughout delivery and lactation and determining its effect on the birth weight, survival, and growth of the offspring during the first 3 weeks of life.

In some instances a multigenerational study may be chosen, often in place of segment III studies, to determine the effects of chemicals on the reproductive system. At least 3 dosage levels are given to groups of 25 female and 25 male rats shortly after weaning (30–40 days of age). These rats are referred to as the  $F_0$  generation. Dosing continues throughout breeding (about 140 days of age), gestation, and lactation. The offspring ( $F_1$  generation) have



thus been exposed to the chemical in utero, via lactation, and in the feed thereafter. When the  $F_1$  generation is about 140 days old, about 25 females and 25 males are bred to produce the  $F_2$  generation, and administration of the chemical is continued. The  $F_2$  generation is thus also exposed to the chemical in utero and via lactation. The  $F_1$  and  $F_2$  litters are examined as soon as possible after delivery. The percentage of  $F_0$  and  $F_1$  females that get pregnant, the number of pregnancies that go to full term, the litter size, the number of still-born, and the number of live births are recorded. Viability counts and pup weights are recorded at birth and at 4, 7, 14, and 21 days of age. The fertility index (percentage of mating resulting in pregnancy), gestation index (percentage of pregnancies resulting in live litters), viability index (percentage of animals that survive 4 days or longer), and lactation index (percentage of animals alive at 4 days that survived the 21-day lactation period) are then calculated. Gross necropsy and histopathology are performed on some of the parents ( $F_0$  and  $F_1$ ), with the greatest attention being paid to the reproductive organs, and gross necropsy is performed on all weanlings.

The International Conference on Harmonization (ICH) guidelines provide for flexible guidelines that address 6 "ICH stages" of development: premating and conception (stage A), conception to implantation (stage B), implantation to closure of the hard palate (stage C), closure of the hard palate to end of pregnancy (stage D), birth and weaning (stage E), and weaning to sexual maturity (stage F). All of these stages are covered in the segment I to segment III studies described above (Christian, 2008).

Numerous short-term tests for teratogenicity have been developed (Faustman, 1988). These tests utilize whole-embryo culture, organ culture, and primary and established cell cultures to examine developmental processes and estimate the potential teratogenic risks of chemicals. Many of these in utero test systems are under evaluation for use in screening new chemicals for teratogenic effects. These systems vary in their ability to identify specific teratogenic events and alterations in cell growth and differentiation. In general, the available assays cannot identify functional or behavioral teratogens (Faustman, 1988).

## Mutagenicity

Mutagenesis is the ability of chemicals to cause changes in the genetic material in the nucleus of cells in ways that allow the changes to be transmitted during cell division. Mutations can occur in either of 2 cell types, with substantially different consequences. Germinal mutations damage DNA in sperm and ova, which can undergo meiotic division and therefore have the potential for transmission of the mutations to future generations. If mutations are present at the time of fertilization in either the egg or the sperm, the resulting combination of genetic material may not be viable, and the death may occur in the early stages of embryonic cell division. Alternatively, the mutation in the genetic material may not affect early embryogenesis but may result in the death of the fetus at a later developmental period, resulting in abortion. Congenital abnormalities may also result from mutations. Somatic mutations refer to mutations in all other cell types and are not heritable but may result in cell death or transmission of a genetic defect to other cells in the same tissue through mitotic division. Because the initiating event of chemical carcinogenesis is thought to be a mutagenic one, mutagenic tests are often used to screen for potential carcinogens.

Numerous in vivo and in vitro procedures have been devised to test chemicals for their ability to cause mutations. Some genetic alterations are visible with the light microscope. In this case, cytogenetic analysis of bone marrow smears is used after the animals have been exposed to the test agent. Because some mutations are

incompatible with normal development, the mutagenic potential of a chemical can also be evaluated by the dominant lethal test. This test is usually performed in rodents. The male is exposed to a single dose of the test compound and then is mated with 2 untreated females weekly for 8 weeks. The females are killed before term, and the number of live embryos and the number of corpora lutea are determined.

The test for mutagens that has received the widest attention is the *Salmonella*/microsome test developed by Ames *et al.* (1975). This test uses several mutant strains of *Salmonella typhimurium* that lack the enzyme phosphoribosyl ATP synthetase, which is required for histidine synthesis. These strains are unable to grow in a histidine-deficient medium unless a reverse or back mutation to the wild type has occurred. Other mutations in these bacteria have been introduced to enhance the sensitivity of the strains to mutagenesis. The 2 most significant additional mutations enhance penetration of substances into the bacteria and decrease the ability of the bacteria to repair DNA damage. Because many chemicals are not mutagenic or carcinogenic unless they are biotransformed to a toxic product by enzymes in the endoplasmic reticulum (microsomes), rat liver microsomes are usually added to the medium containing the mutant strain and the test chemical. The number of reverse mutations is then quantified by the number of bacterial colonies that grow in a histidine-deficient medium.

Strains of yeast have recently been developed that detect genetic alterations arising during cell division after exposure to nongenotoxic carcinogens as well as mutations that arise directly from genotoxic carcinogens. This test identifies deletions of genetic material that occur during recombination events in cell division that may result from oxidative damage to DNA, direct mutagenic effects, alterations in fidelity of DNA repair, and/or changes in cell cycle regulation (Galli and Schiestl, 1999). Mutagenicity is discussed in detail in Chap. 9.

With the advent of techniques that readily allow manipulation of the mouse genome, transgenic animals have been developed that allow for in vivo assessment of mutagenicity of compounds. For example, 2 commercially available mouse strains, the "MutaMouse" and "Big Blue," contain the *lac* operon of *E. coli* that has been inserted into genomic DNA using a lambda phage to DNA to produce a recoverable shuttle vector. Stable, homozygous strains of these transgenic animals (both mice and rats have been engineered) can be exposed to potential mutagenic agents. Following in vivo exposure, the target *lac* genes can be recovered from virtually any cell type or organ and analyzed for mutations (Brusick *et al.*, 2008).

## Oncogenicity Bioassays

Oncogenicity studies are both time consuming and expensive, and are usually only done when there is reason to suspect that a chemical may be carcinogenic, or when there may be wide spread, long-term exposures to humans (eg, widely used food additives, drinking water contaminants, or pharmaceuticals that are likely to be administered repeatedly for long periods of time). Chemicals that test positive in several mutagenicity assays are likely to be carcinogenic, and thus are frequent candidates for oncogenicity bioassay assessment. In the United States, the National Toxicology Program (NTP) has the primary responsibility for evaluating non-drug chemicals for carcinogenic potential. For pharmaceuticals, the FDA may require the manufacturer to conduct oncogenicity studies as part of the preclinical assessment, depending on the intended use of the drug, and the results of mutagenicity assays and other toxicological data.



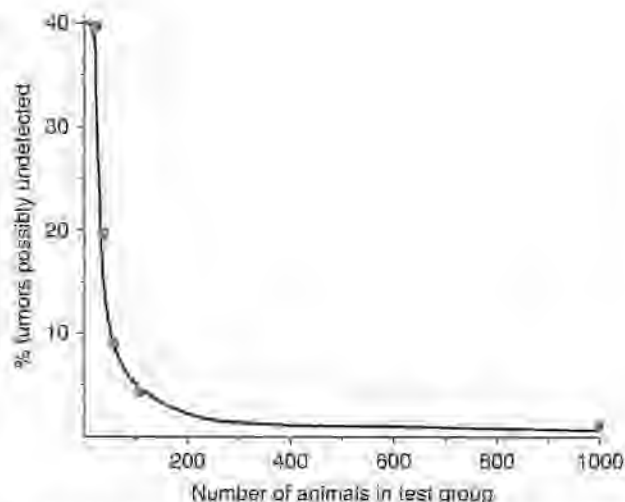


Figure 2-14. Statistical limitations in the power of experimental animal studies to detect tumorigenic effects.

Studies to evaluate the oncogenic (carcinogenic) potential of chemicals are usually performed in rats and mice and extend over the average lifetime of the species (18 months to 2 years for mice, 2–2.5 years for rats). To ensure that 30 rats per dose survive the 2-year study, 60 rats per group per sex are often started in the study. Both gross and microscopic pathological examinations are made not only on animals that survive the chronic exposure but also on those that die prematurely. The use of the MTD in carcinogenicity has been the subject of controversy. The premise that high doses are necessary for testing the carcinogenic potential of chemicals is derived from the statistical and experimental design limitations of chronic bioassays. Consider that a 0.5% increase in cancer incidence in the United States would result in over 1 million additional cancer deaths each year—clearly an unacceptably high risk. However, identifying with statistical confidence a 0.5% incidence of cancer in a group of experimental animals would require a minimum of 1000 test animals, and this assumes that no tumors were present in the absence of exposure (zero background incidence).

Fig. 2-14 shows the statistical relationship between minimum detectable tumor incidence and the number of test animals per group. This curve shows that in a chronic bioassay with 50 animals per test group, a tumor incidence of about 8% could exist even though no animals in the test group had tumors. This example assumes that there are no tumors in the control group. These statistical considerations illustrate why animals are tested at doses higher than those that occur in human exposure. Because it is impractical to use the large number of animals that would be required to test the potential carcinogenicity of a chemical at the doses usually encountered by people, the alternative is to assume that there is a relationship between the administered dose and the tumorigenic response and give animals doses of the chemical that are high enough to produce a measurable tumor response in a reasonable size test group, such as 40 to 50 animals per dose. The limitations of this approach are discussed in Chap. 4. For nonmutagenic pharmaceutical agents, ICH S1C provides the following guidance on dose selection for oncogenicity studies: “The doses selected for rodent bioassays for non-genotoxic pharmaceuticals should provide an exposure to the agent that (1) allow an adequate margin of safety over the human therapeutic exposure, (2) are tolerated without significant chronic physiological dysfunction and are compatible with good survival, (3) are guided by a comprehensive set of animal and human data that focus broadly on the properties of the agent and the suitability of the animal (4) and permit data interpretation in the context of clinical use.”

Another approach for establishing maximum doses for use in chronic animal toxicity testing of drugs is often used for substances for which basic human pharmacokinetic data are available (eg, new pharmaceutical agents that have completed phase I clinical trials). For chronic animal studies performed on drugs where single-dose human pharmacokinetic data are available, a daily dose that would provide an area under the curve (AUC) in laboratory animals equivalent to 25 times the AUC in humans given the highest (single) daily dose to be used therapeutically may be used, rather than the MTD. Based on a series of assumptions regarding allometric scaling between rodents and humans (Table 2-2), the ICH noted that it may not be necessary to exceed a dose of 1500 mg/kg per day where there is no evidence of genotoxicity, and where the maximum recommended human dose does not exceed 500 mg per day.

Most regulatory guidelines require that both benign and malignant tumors be reported in oncogenicity bioassays. Statistical increases above the control incidence of tumors (either all tumors or specific tumor types) in the treatment groups are considered indicative of carcinogenic potential of the chemical unless there are qualifying factors that suggest otherwise (lack of a dose response, unusually low incidence of tumors in the control group compared with “historic” controls, etc; Huff, 1999). Thus, the conclusion as to whether a given chronic bioassay is positive or negative for carcinogenic potential of the test substance requires careful consideration of background tumor incidence. Properly designed chronic oncogenicity studies require that a concurrent control group matched for variables such as age, diet, and housing conditions be used. For some tumor types, the “background” incidence of tumors is surprisingly high. Fig. 2-15 shows the background tumor incidence for

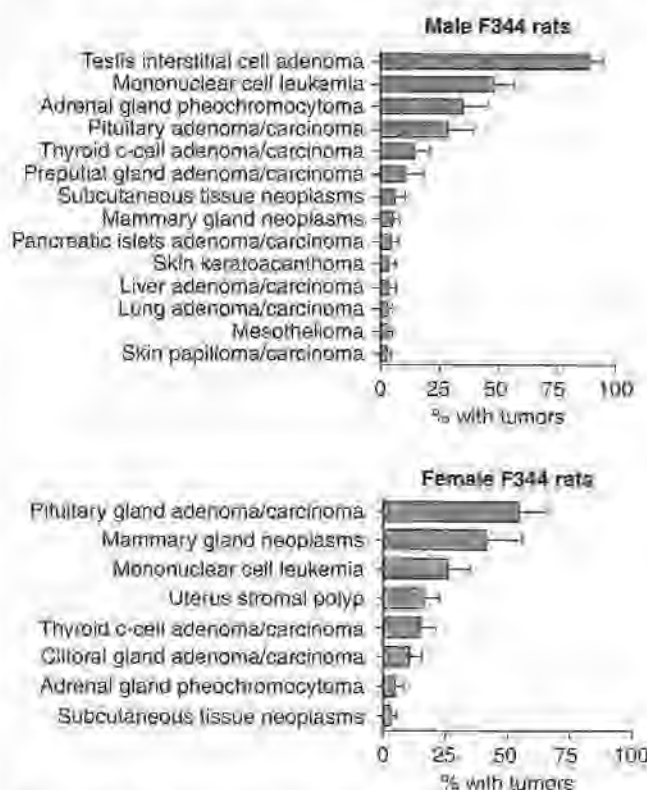


Figure 2-15. Most frequently occurring tumors in untreated control rats from recent NTP 2-year rodent carcinogenicity studies. The values shown represent the mean  $\pm$  SD of the percentage of animals developing the specified tumor type at the end of the 2-year study. The values were obtained from 27 different studies involving a combined total of between 1319 and 1353 animals per tumor type.



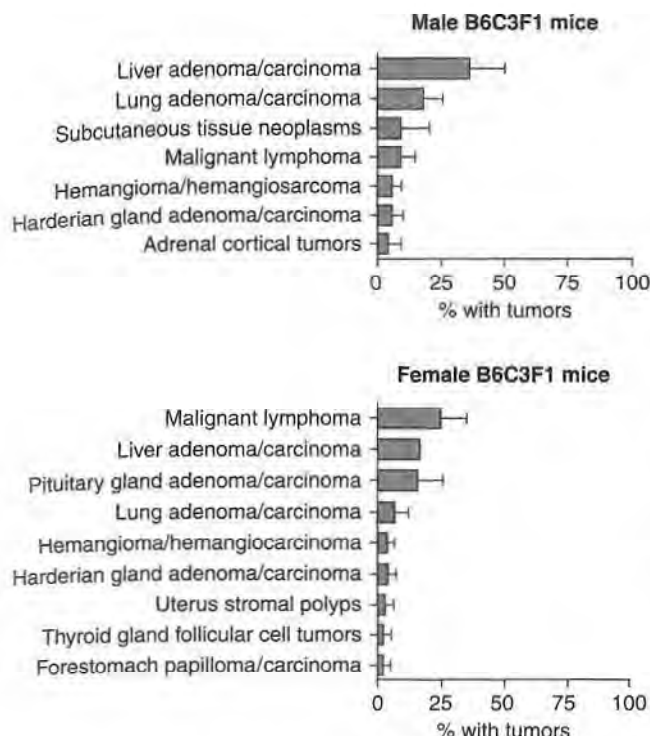


Figure 2-16. Most frequently occurring tumors in untreated control mice from recent NTP 2-year rodent carcinogenicity studies. The values shown represent the mean  $\pm$  SD of the percentage of animals developing the specified tumor type at the end of the 2-year study. The values were obtained from 30 different studies involving a total of between 1447 and 1474 animals per tumor type.

various tumors in male and female F344 rats used in 27 NTP 2-year rodent carcinogenicity studies. The data shown represent the percent of animals in control (nonexposed) groups that developed the specified tumor type by the end of the 2-year study. These studies involved more than 1300 rats of each sex. Fig. 2-16 shows similar data for control (nonexposed) male and female B6C3F1 mice from 30 recent NTP 2-year carcinogenicity studies and includes data from over 1400 mice of each sex. There are several key points that can be derived from these summary data:

1. Tumors, both benign and malignant, are not uncommon events in animals even in the absence of exposure to any known carcinogen.
2. There are numerous different tumor types that develop "spontaneously" in both sexes of both rats and mice, but at different rates.
3. Background tumors that are common in 1 species may be uncommon in another (eg, testicular interstitial cell adenomas are very common in male rats but rare in male mice; liver adenomas/carcinomas are about 10 times more prevalent in male mice than in male rats).
4. Even within the same species and strain, large gender differences in background tumor incidence are sometimes observed (eg, adrenal gland pheochromocytomas are about 7 times more prevalent in male F344 rats than in female F344 rats; lung and liver tumors are twice as prevalent in male B6C3F1 mice as in female B6C3F1 mice).
5. Even when the general protocols, diets, environment, strain and source of animals, and other variables are relatively constant, background tumor incidence can vary widely, as shown by the relatively large SDs for some tumor types in the NTP

bioassay program. For example, the range in liver adenoma/carcinoma incidence in 30 different groups of unexposed (control) male B6C3F1 mice went from a low of 10% to a high of 68%. Pituitary gland adenomas/carcinomas ranged from 12% to 60% and 30% to 76% in unexposed male and female F344 rats, respectively, and from 0% to 36% in unexposed female B6C3F1 mice.

Taken together, these data demonstrate the importance of including concurrent control animals in such studies. In addition, comparisons of the concurrent control results to "historic" controls accumulated over years of study may be important in identifying potentially spurious "false-positive" results. The relatively high variability in background tumor incidence among groups of healthy, highly inbred strains of animals maintained on nutritionally balanced and consistent diets in rather sterile environments highlights the dilemma in interpreting the significance of both positive and negative results in regard to the human population, which is genetically diverse, has tremendous variability in diet, nutritional status, and overall health, and lives in an environment full of potentially carcinogenic substances, both natural and human-made.

Finally, it should be noted that both inbred and outbred strains have distinct background tumor patterns and the NTP and most other testing programs select strains based on the particular needs of the agent under study. For example, the NTP used the Wistar rat for chemicals that may have the testis as a target organ, based on acute, subchronic, or other bioassay results. Similarly, the NTP used the Sprague-Dawley strain of rat in studies of estrogenic agents such as genistein because its mammary tumors are responsive to estrogenic stimulation, as are humans'.

## Neurotoxicity Assessment

Neurotoxicity or a neurotoxic effect is defined as an adverse change in the chemistry, structure, or function of the nervous system following exposure to a chemical or physical agent. The structure, function, and development of the nervous system and its vulnerability to chemicals are examined in Chap. 16. When evaluating the potential neurological effects of a compound, effects may be on the central or peripheral nervous system or related to exposure that occurred during development or as an adult. The developing nervous system is particularly sensitive to chemical exposures (see Chap. 10).

In vitro systems often using cell culture techniques are a rapidly developing area of neurotoxicity assessment. Specific cell lines are available to examine effects on neuron or glial cells such as proliferation, migration, apoptosis, synaptogenesis, and other end points. In vitro assays have a number of potential advantages including minimizing the use of animal, lower costs, and adaptable to high-throughput screening. It is also possible to use an in vitro model to examine the interaction of chemicals, such as food additives, on neuronal cells (Lau *et al.*, 2006). The principles and challenges of in vitro neurotoxicity testing are well described (Claudio, 1992; Tiffany-Castiglioni, 2004).

Procedures for the neurobehavioral evaluation of animals were initially developed as part of the scientific investigation of behavioral motivation. Some of these procedures were then used to evaluate the neuropharmacological properties of new drugs. Now animals are commonly used to evaluate the neurotoxic properties of chemicals. A wide range of adult and developmental animal tests are used to assess neurobehavioral function. In addition, neuropathological assessment is an important part of the neurotoxicity evaluation and



best practices have been developed for developmental neurotoxicity (DNT) (Bolon *et al.*, 2006). Irwin developed a basic screen for behavioral function in mice (Irwin, 1968), which was subsequently refined to the functional observational battery (FOB) (Moser, 2000). The FOB can also be used in the evaluation of drug safety (Redfern *et al.*, 2005).

The US EPA established a protocol for the evaluation of DNT in laboratory animals (US EPA 870.6300 and OECD 426) (EPA, 1998; OECD, 2004). These protocols include tests of neurobehavioral function, such as auditory startle, learning and memory function, changes in motor activity, and neuropathological examination and morphometric analysis. Methods and procedures for DNT evaluation are well established (Claudio *et al.*, 2000; Cory-Slechta *et al.*, 2001; Dorman *et al.*, 2001; Garman *et al.*, 2001; Miles and Ferenc, 2001). Recent studies examine the neurotoxicity of multiple chemical exposures in animals (Moser *et al.*, 2006). Methods are also available to examine cognitive measures on weanling rodents in DNT studies (Ehman and Moser, 2006). Nonhuman primates have been invaluable in evaluating the effects of neurotoxicants and the risk assessment process (Burbacher and Grant, 2000). Sophisticated assessment of operant behavior, and learning and memory assessment of rodents, has been used to evaluate the effects of lead (Cory-Slechta, 1995, 1996, 2003). Monkeys can also be used to evaluate the low-level effects of neurotoxicants such as mercury on vision, auditory function, and vibration sensitivity (Burbacher *et al.*, 2005; Rice and Gilbert, 1982, 1992, 1995). There is remarkable concordance between human and animal neurotoxicity assessment, for example, in lead, mercury, and PCBs (Rice, 1995).

Human testing for the neurological effects of occupational exposures to chemicals (Anger, 2003; Farahat *et al.*, 2003; Kamel *et al.*, 2003; McCauley *et al.*, 2006), and even the neurotoxic effects of war (Binder *et al.*, 1999, 2001), is advancing rapidly. These methods have also been applied to Hispanic workers (Rohlman *et al.*, 2001b) and populations with limited education or literacy (Rohlman *et al.*, 2003). The WHO has also recommended a test battery for humans (Anger *et al.*, 2000). There are also neurobehavioral test batteries for assessing children (Rohlman *et al.*, 2001a). Evaluation of the childhood neurological effects of lead (Lanphear *et al.*, 2005; Needleman and Bellinger, 1991) and mercury (Myers *et al.*, 2000) has added enormously to our understanding of the health effects of these chemicals and to the methodology of human neurobehavioral testing.

In summary, the neurotoxicological evaluation is an important aspect of developing risk assessments for environmental chemicals and drugs.

## Immunotoxicity Assessment

Under normal conditions, the immune system is responsible for host defense against pathogenic infections and certain cancers. However, environmental exposures can alter immune system development and/or function and lead to hypersensitivity, autoimmunity, or immunosuppression, the outcome of which may be expressed as a pathology in most any organ or tissue (see Chap. 12). Our understanding of the biological processes underlying immune system dysfunction remains incomplete. However, advances in molecular biology (including use of transgenic/knockout mice), analytic methods (including gene expression arrays and multiparameter flow cytometry), animal models (including adoptive transfers in immunocompromised mice and host resistance to viral, bacterial, or tumor cell challenge), and other methods are greatly advancing our knowledge.

From a toxicologist's perspective, evaluation of immune system toxicity represents special challenges. Development of hypersensitivity can take various forms, depending on the mechanism underlying the associated immune response, and standard assumptions regarding dose-response relationships may not necessarily apply. For example, a single or incidental exposure to beryllium has been associated with chronic beryllium disease in some individuals. We are only just beginning to understand the biological basis underlying such individual susceptibility. In the case of chronic beryllium disease, a genetic polymorphism in a gene involved in antigen recognition may be associated with increased susceptibility (see Bartell *et al.*, 2000). Although our ability to predict immunogenicity remains poor, research efforts are continuing to identify aspects of the chemical and the individual that confer immunogenicity and underlie hypersensitivity. For example, the increasing incidence of allergic asthma among preschool-age children in the United States since the 1980s may be associated with exposure to allergens (eg, dust mites, molds, and animal dander), genetic factors, and other factors in the in utero and postnatal environment (see Donovan and Finn, 1999; Armstrong *et al.*, 2005).

Immunosuppression is another form of immune system toxicity, which can result in a failure to respond to pathogenic infection, a prolonged infection period, or expression of a latent infection or cancer. Various chemicals have been associated with immunosuppression. Broad-spectrum and targeted immunosuppressive chemicals are designed and used therapeutically to reduce organ transplant rejection or suppress inflammation. However, a large number of chemicals have been associated with immunosuppression, including organochlorine pesticides, diethylstilbestrol, lead, and halogenated aromatic hydrocarbons (including TCDD), and exposures that occur during critical stages may present special risk to development (Holladay, 2005).

Autoimmunity is a specific immune system disorder in which components of the immune system attack normal (self) tissues. Cases of autoimmunity have been reported for a wide range of chemicals including therapeutic drugs, metals, pesticides, and solvents. As with other forms of immune system toxicity, autoimmunity can present in most any tissue.

Finally, new forms of immunotoxicity are appearing based on novel forms of clinical therapy and immunomodulation. These include the variously classified "tumor lysis syndromes" and "cytokine storms" that arise from massive cytokine dysregulation. A recent example involved 6 healthy volunteers who had enrolled in a phase I clinical trial in the United Kingdom who developed a severe cytokine response to an anti-CD28 monoclonal antibody leading to systemic organ failures (Bhagal and Combes, 2006). Such cases are stark reminders of the challenges we face in understanding how the immune system is regulated, developing reliable test systems for identifying such risks prior to human use, and developing safe means for testing these agents in humans.

As described in Chap. 12, current practice for evaluating potential toxic effects of xenobiotic exposures on the immune system involves a tiered approach to immunotoxicity screening (Luster *et al.*, 2003). This tiered approach is generally accepted worldwide in the registration of novel chemical and therapeutic products. Most recently, final guidance to the pharmaceutical industry was published in April 2006 by the ICH of Technical Requirements for Registration of Pharmaceuticals for Human Use (Table 2-3). This guidance, which applies to the nonclinical (animal) testing of human pharmaceuticals, is the accepted standard in the United States, EU, and Japan, and demonstrates the continued commitment by these regulatory bodies to understand the potential risks posed by novel therapeutics.



Tiered testing relies on the concept that standard toxicity studies can provide good evidence for immunotoxicity when considered with known biological properties of the chemical, including structural similarities to known immunomodulators, disposition, and other clinical information, such as increased occurrence of infections or tumors. Evaluation of hematological changes, including differential effects on white blood cells and immunoglobulin changes, and alterations in lymphoid organ weights or histology, can provide strong evidence of potential effects to the immune system. Should such evaluations indicate a potential effect on immune system function, more detailed evaluations may be considered, including the evaluation of functional effects (eg, T-cell-dependent antibody response or natural killer cell activity), flow cytometric immunophenotyping, or host resistance studies. Thus, as with other areas of toxicology, the evaluation of immune system toxicity requires the toxicologist to be vigilant in observing early indications from a variety of sources in developing a weight-of-evidence assessment regarding potential injury/dysfunction.

### Other Descriptive Toxicity Tests

Most of the tests described above will be included in a "standard" toxicity testing protocol because they are required by the various regulatory agencies. Additional tests may be required or included in the protocol to provide information relating a special route of exposure, such as inhalation. Inhalation toxicity tests in animals usually are carried out in a dynamic (flowing) chamber rather than in static chambers to avoid particulate settling and exhaled gas complications. Such studies usually require special dispersing and analytic methodologies, depending on whether the agent to be tested is a gas, vapor, or aerosol; additional information on methods, concepts, and problems associated with inhalation toxicology is provided in Chaps. 15 and 28. The duration of exposure for inhalation toxicity tests can be acute, subchronic, or chronic, but acute studies are more common with inhalation toxicology. Other special types of animal toxicity tests include toxicokinetics (absorption, distribution, biotransformation, and excretion), the development of appropriate antidotes and treatment regimens for poisoning, and the development of analytic techniques to detect residues of chemicals in tissues and other biological materials.

### TOXICOGENOMICS

In the past decade, numerous new genome-based technologies have become available that allow for the large-scale analysis of biological responses to external stimuli. Traditional scientific approaches to elucidate the biochemical and molecular effects of toxic substances focused largely on examining biochemical pathways that were logically connected to observed responses identified through gross pathology, histology, blood chemistry, or behavioral observations. Such "hypothesis-driven" research into understanding mechanism of action remains a mainstay of current scientific investigations in toxicology. However, technologies now available allow one to examine the entire "universe" of biological responses to a toxic substance (Fig. 2-17). These new "hypothesis-generating" technologies include genomics (characterization of much or all of the genome of an organism), transcriptomics (characterization of most or all of the messenger RNAs [mRNAs], or transcriptome, expressed in a given cell/tissue), proteomics (characterization of most or all of the proteins expressed in a given cell/tissue), and metabolomics (characterization of most or all of the small molecules in a cell or tissue, including substrates, products, and cofactors of enzyme reactions). Other "omics" approaches (eg, "lipidomics,"

"nutrigenomics") are being devised to look broadly at the biological response of an organism to change. The integration of all of these levels of molecular function (genomics, transcriptomics, proteomics, metabolomics, etc) to the understanding of how a living organism functions at the cellular level is sometimes referred to as "systems biology" (Weston and Hood, 2004). Because each level of analysis generates a very large quantity of data, the collection, organization, evaluation, and statistical analysis is in itself an enormous undertaking. The field of "bioinformatics" has been developed to address the many computational and statistical challenges of "omics" data. In the field of toxicology, the term "toxicogenomics" is used to define the area of research that "combines transcript, protein and metabolite profiling with conventional toxicology to investigate the interaction between genes and environmental stress in disease causation" (Waters and Fostel, 2004). A conceptual model for how the various new "omics" technologies can be incorporated into toxicological evaluation is shown in Fig. 2-17.

### Genomics

The genome of an organism represents the full complement of genes that are determined at fertilization by the combination of the parental DNA. Thus, each cell of an organism has the same genome, characterized by the nucleotide sequences inherited from its parents. The human genome consists of approximately 3 billion base pairs of deoxyribonucleotides. Within the human genome, there is, on average, about 0.1% variability in DNA sequence between any 2 individuals, and it is these differences that contribute to the uniqueness of each person. Most of this variability exists as "SNPs," although larger segments of DNA may be variable between individuals, including the duplication or loss of entire genes. The identification of particular genetic variants, such as the GSTM1 polymorphism, which might contribute to interindividual differences in susceptibility to chemicals or other environmental factors discussed previously, represents a relatively new and growing area of study that aims to understand the complex interactions between the human genome and the environment (Costa and Eaton, 2006).

Although the genome provides the blueprint for biological function, in order for the genomic information to be utilized in a cell, it must be expressed. Expression of the genome occurs when the coding sequence of DNA is converted to mRNA. For any given cell, transcription of the genomic information contained in that cell is only partial. It is the differential expression of genes in a given cell that is largely responsible for the diverse function of the thousands of different cells, tissues, and organs that constitute an individual organism. Thus, understanding which genes are expressed in a given tissue, at what level, and how toxicants perturb the "transcriptome" is of great relevance to toxicology. In addition to coding for mRNAs that provide the blueprint for protein synthesis, genomic DNA also generates small interfering RNAs (siRNA, microRNAs) that are biologically active and can participate in the regulation of gene expression.

### Epigenetics/Epigenomics

The expanding research into the relatively new field of epigenomics will have important implications for public health and toxicology. The concept of epigenetics, meaning something acting "above or in addition" to genes, was proposed many decades ago, although the application to the full genome (epigenomics) rather than to single or a few genes (epigenetics) is new. Conrad Hal Waddington first postulated in the 1930s that it was not just the genes that shaped development but also the environment that shapes the genes



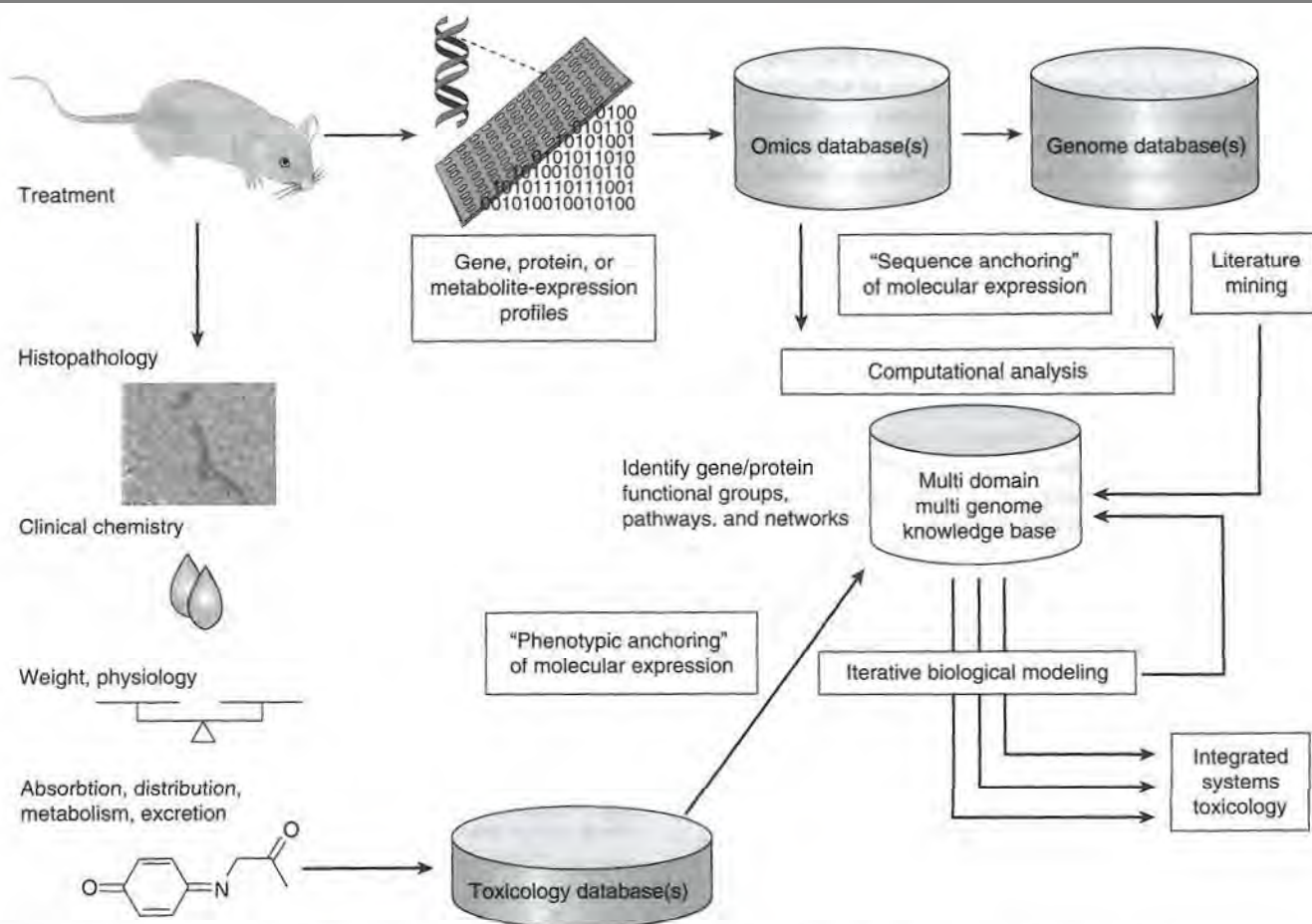


Figure 2-17. Conceptual approach for incorporating "omics" technologies and resulting large databases into toxicological evaluation. Data from experiments that evaluate the effects of a chemical on global patterns of gene expression (transcriptomics), protein content (proteomics), and small molecules/metabolites (metabonomics/metabolomics), combined with genomic information from both the test species (eg, rats, mice) and the target species of interest (eg, humans), are analyzed by computational tools (bioinformatics) for unique or potentially predictive patterns of toxicity. Essential to the use of omics data for predictive toxicology/safety assessment is the ability to reliably tie observed omics patterns to traditional measures of toxicity, such as histopathology and clinical chemistry (phenotypic anchoring). (From Waters and Postel, 2004, with permission.)

(Holliday, 2006). Understanding a possible mechanism had to wait for a far deeper understanding of DNA and its role in development. Epigenetics has been defined in various ways, with perhaps the strictest definition being "a mitotically or meiotically heritable change in gene expression that occurs independently of an alteration in DNA sequence" (Youngson and Whitelaw, 2008). Typically gene expression is silenced or suppressed, or in some instances activated, by DNA methylation or histone deacetylation—changes that do not alter the nucleotide sequence of the silenced genes (Fig. 2-18). Epigenetic changes can potentially be transgenerational, as suggested in some animal models, which has important implications for toxicological assessment (Rosenfeld, 2010; Skinner, 2011). Given the growing recognition of epigenetics as a means by which environmental factors can alter biological responses, genomic analyses in toxicology may also include techniques to identify toxicant-induced changes in DNA methylation patterns (Watson and Goodman, 2002; LeBaron *et al.*, 2010).

Although classical approaches to toxicology have thoroughly documented the potential for a variety of environmental toxicants, such as thalidomide, alcohol, lead, mercury, and PCBs, to cause adverse effects on the developing organism, more subtle epigenetic changes, which are not associated with either cytotoxicity or mutations, can also result from environmental exposures and

thus may have important toxicological implications. Epigenetic changes have been demonstrated to occur from exposure to a variety of environmental hazards, including tobacco smoke, metals, alcohol, phthalates, and BPA (Cheng *et al.*, 2012; Perera and Herbstman, 2011; Bernal and Jirtle, 2010; Baccarelli and Bollati, 2009). Furthermore, epigenetic changes can occur through nutrition, methyl content of diet, intake of folic acid and vitamins, or even social and maternal behavior toward the offspring (Cummings *et al.*, 2010). Epigenetic changes have been causally implicated in cancer, neurodevelopment disorders, autoimmune diseases, diabetes and metabolic disorders, asthma, behavioral disorders, and endocrine disorders (Godfrey *et al.*, 2011; Nystrom and Mutanen, 2009; Zhang and Ho, 2011; Attig *et al.*, 2010). There is also concern chemicals in the environment may induce epigenetic changes in wildlife that could be an important consideration in ecotoxicology (Vandegheuchte and Janssen, 2011; Head *et al.*, 2012). Thus, epigenetic changes induced by xenobiotics, dietary factors, and maternal behavior have important implications for safety assessment and risk assessment for xenobiotics (LeBaron *et al.*, 2010; Goodman *et al.*, 2010; Szyf, 2007).

Thus, it is now evident that methylation of DNA is an important determinant of gene expression in cells and tissues, and exogenous chemicals can interfere with transcriptional function



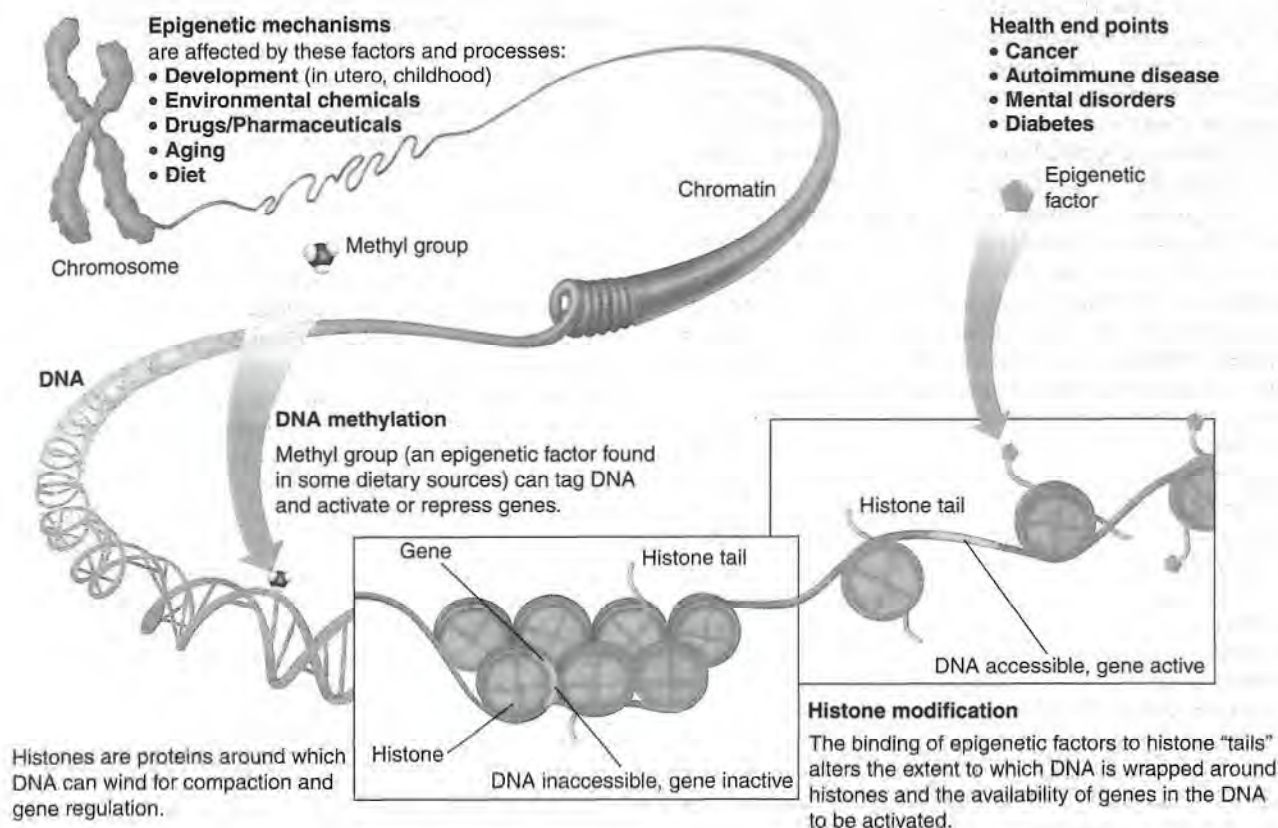


Figure 2-18. Process and consequence of epigenetic regulation of gene expression (National Institute of Health).

via alternating DNA methylation (Watson and Goodman, 2002). Importantly, although such epigenetic changes do not result in the alteration of the genomic sequence, they theoretically can result in heritable phenotypic changes; although proof of multigenerational epigenetic changes from environmental exposures has yet to be demonstrated in humans (Baccarelli and Bollati, 2009), several animal models have demonstrated transgenerational epigenetic changes (Skinner, 2011). Thus, genomic analyses in toxicology may also include techniques to identify toxicant-induced changes in DNA methylation patterns to access epigenetic changes and the potential consequences (Watson and Goodman, 2002; Szyf, 2007).

## Transcriptomics

Among the first changes that a cell will exhibit following exposure to a toxic substance is a change in gene expression. The transcriptome (all of the mature mRNA species present in a cell at a given point in time) is dynamic, and represents the steady state between the rate of synthesis (transcription) and degradation of mRNAs in a cell. Toxicologists have utilized the so-called Northern blot analysis to assess the level of expression of individual genes in cells or tissues for decades. The "reverse transcriptase polymerase chain reaction" (RT-PCR) allows one to quantitatively measure the relative number of mRNA species in a sample for specific genes. Using general primers, it is also possible to amplify the entire transcriptome quantitatively to make many complete copies of the transcriptome in a test tube. Thus, large amounts of material for analysis can be obtained from a relatively small number of cells. Finally,

using microarray technologies, where tens of thousands of unique oligonucleotides (or cDNAs) are anchored on a solid matrix, toxicologists can now quantitatively assess the expression of thousands of unique mRNAs in a single sample, thus capturing an "expression profile" of the entire transcriptome in 1 analysis.

There is great promise that gene expression profiles may be used to provide signatures of specific types of toxic responses, such as a cellular response to DNA damage or oxidative stress. There is also hope that such signature changes in gene expression could be used to facilitate more accurate cross-species extrapolation, allowing comparison of, for example, toxicant-induced changes in gene expression in rat hepatocytes with that of human hepatocytes under identical experimental conditions. However, 1 of the major challenges in toxicogenomics is the recognition that transcriptional regulation is highly dynamic, and that gene expression profiles can change dramatically with both dose and time. Because microarray experiments are relatively expensive and highly data intensive, it becomes both costly and challenging to conduct and analyze experiments with extensive dose and time course data (although costs are declining). Although changes in gene expression often contribute to, or are reflective of, phenotypic changes that occur in response to a toxic substance, the transcriptome is still somewhat far removed from the ultimate biochemical functions that dictate the actual biological function of the cell. Because the functional expression of a gene generally requires the translation of the mRNA to a protein, there is also great interest in looking at the "proteome"—the entire complement of proteins that are present in a cell or tissue at a given point in time.



Analysis of the proteome of a cell or tissue is much more difficult than analysis of the transcriptome, primarily because it is not yet possible to “amplify” the number of copies of proteins in a cell. Furthermore, unambiguous identification of specific proteins is much more difficult than that for individual mRNAs. Identification of specific proteins is generally done using a combination of separation techniques (eg, 2D gel electrophoresis, high-performance liquid chromatography), followed by tandem mass spectrometry for identification (Aebersold and Mann, 2003). Because of size limitations for accurate mass spectrometry, protein mixtures are usually digested to smaller peptide fragments. The mixture of peptide fragments is resolved into individual components, and the identity of the specific peptides is determined based on high-resolution mass analysis and sequential degradation (sequential loss of single amino acids) of the peptides by various means (Aebersold and Mann, 2003). The large and complex set of peptide mass fragments is then analyzed by computers and compared with a large database of mass fragments of known peptides/proteins. Because as few as 5 amino acid sequences may provide unique identification of a specific protein, the presence and relative abundance of specific proteins in a sample can then be reconstructed through bioinformatic analyses. As with transcriptomics, it is hoped that changes in protein expression can be used as specific biomarkers for particular types of toxic responses. Of course, such conceptual approaches have been used for years, for example, use of serum transaminase proteins as indicators of liver damage, or the presence of prostate-specific antigen (PSA) in serum as a potential biomarker of early stage prostate hyperplasia or cancer. The potential power of proteomics lies in the ability to identify unique patterns of protein expression, or identification of unique proteins or peptides, that are predictive of early toxic response or later development of disease.

### Metabonomics/Metabolomics

These 2 terms are often used interchangeably to describe the analysis of the “universe” of small molecules that serve as substrates, products, and cofactors of the milieu of enzymatic reactions and other metabolic processes that define living cells, and thus the organism. Metabonomics has been defined as “the comprehensive and simultaneous systematic profiling of metabolite levels and their systematic and temporal change through such effects on diet, lifestyle, environment, genetic and pharmaceuticals, both beneficial and adverse, in whole organisms” (Lindon *et al.*, 2003, 2006). The term “metabolomics” has been used principally in studies in plants and in vitro or single-cell systems (Fiehn, 2002). Regardless of the specific term used (metabonomics will be used here), the concept of quantitatively analyzing toxicant-induced changes in the “metabolic profile” (the “metabonome”) of a cell, tissue, or body fluid in some ways represents the “Holy Grail” of toxicogenomics, because the changes in these small molecules must represent a biologically relevant integration of all of the molecular, biochemical, and cellular perturbations that lead to the development of toxicity (Fig. 2-17). In other words, changes in the metabonome should reflect the biologically relevant changes in gene transcription, translation, protein function, and other cellular processes, including temporal and adaptive responses, while ignoring biologically irrelevant changes in these factors. Although conceptually superior to either transcriptomics or proteomics for predictive toxicology, metabonomics lags significantly in technological development of readily accessible tools for thorough analysis of the metabonome.

Two approaches for identifying and measuring hundreds, or even thousands, of small molecules in biological samples have emerged—nuclear magnetic resonance (NMR) and mass spectrometry (Lindon *et al.*, 2003, 2006). Both have their advantages and limitations, and it is likely that the most successful approaches to applying metabonomics to toxicological problems will utilize both techniques (Pan and Raftery, 2007).

### Bioinformatics

One feature in common among all of the various “omics” technologies is the ability to generate very large volumes of data (literally millions of data points from a single experiment). Both the data management and statistical evaluation of toxicogenomics studies represent an enormous challenge. The emerging field of bioinformatics has developed to address these challenges. Numerous commercial platforms for conducting microarray analysis of the transcriptome are available, and sophisticated software is available for both data management and analysis. One of the major challenges in statistical analysis of large data sets is the large number of “false positives” that will result from multiple comparisons. In a typical gene array experiment, it is not uncommon for an investigator to make >20,000 different comparisons. At the typical “95%” statistical confidence limit, one would expect more than 1000 of the noted differences to occur just by chance alone. Thus, more rigorous statistical methods have been developed to reduce the so-called false discovery rate in such experiments (Storey *et al.*, 2005; Gao, 2006).

### Challenges in Using “Omics” Technologies for Predictive Toxicology and Risk Assessment

A conceptual framework for incorporating these new technologies into toxicology, sometimes referred to as “systems toxicology,” is shown in Fig. 2-18. Several key components of such an approach include: (1) large databases of treatment-specific information, such as results of transcriptomic, proteomic, and metabonomic analyses from target tissues and/or body fluids derived from toxicant-treated animals, (2) genomic databases that describe the DNA sequence information from the species of interest, (3) computational tools that extract information from these and other databases and the published literature to identify critical pathways and networks that are altered by the toxicant treatment, and (4) comparison with traditional toxicological end points to ensure that the observed “omics responses” are closely aligned with the toxicant-related pathophysiology in the animal (histopathology, clinical chemistry, etc)—a process called “phenotypic anchoring” (Waters and Fostel, 2004).

Toxicogenomics tools are becoming indispensable for research aimed at identifying the mechanisms and mode of action of toxic substances. However, the incorporation of such approaches into routine toxicity assessment presents numerous challenges. Numerous working group reports and publications have addressed the challenges of incorporating toxicogenomics data into predictive toxicology and risk assessment (Bammler *et al.*, 2005; Maggioli *et al.*, 2006; Boverhof and Zacharewski, 2006).

One of the major challenges to incorporating toxicogenomic data into risk assessment is related to the highly dynamic processes that preceded an observed toxic response. Traditional measure of toxicity, such as histopathological changes in a tissue, tends to be stable or even irreversible, whereas the myriad of molecular, biochemical, and cellular changes that give rise to the toxic response(s) are highly dynamic, frequently changing by the hour. Thus, the



profiles of mRNAs, proteins, and/or metabolites captured at a single point in time may be dramatically different, depending on the specific point in time the sample was collected. Many of the observed changes may be the result of direct effects of the toxicant on specific targets, whereas others will be compensatory or feedback mechanisms invoked in response to the initial damage. Nevertheless, patterns of change in transcript, protein, and/or metabolite profiles are likely to provide informative "signatures" of toxic response that will be of great value in predictive toxicology. Such approaches may be particularly useful in pharmaceutical development, where toxicogenomic profiles may help to accelerate preclinical evaluation of drug candidates by identifying "class prediction" profiles indicative of certain types of desirable (pharmacological efficacy) as well as adverse (eg, DNA damage, oxidative stress) responses.

Finally, it is likely that the introduction of omics technologies to toxicity testing will eventually contribute to the reduction, refinement, and replacement (the "3Rs") of animals in toxicity testing and product safety evaluations (Kroeger, 2006).

## REFERENCES

- Aebersold R, Mann M. Mass spectrometry-based proteomics. *Nature*. 2003;422:198–207.
- Albert A. *Selective Toxicity*. London: Chapman and Hall; 1973.
- Aldridge WN. The biological basis and measurement of thresholds. *Annu Rev Pharmacol Toxicol*. 1986;26:39–58.
- Allen BC, Kavlock RJ, Kimmel CA, et al. Dose–response assessment for developmental toxicity: II. Comparison of generic benchmark dose estimates with no observed adverse effect levels. *Fundam Appl Toxicol*. 1994a;23:487–495.
- Allen BC, Kavlock RJ, Kimmel CA, et al. Dose–response assessment for developmental toxicity: III. Statistical models. *Fundam Appl Toxicol*. 1994b;23:496–509.
- Ames BN, McCann J, Yamasaki E. Methods for detecting carcinogens and mutagens with the *Salmonella*/mammalian-microsome mutagenicity test. *Mutat Res*. 1975;31:347–364.
- Anger WK. Neurobehavioural tests and systems to assess neurotoxic exposures in the workplace and community. *Occup Environ Med*. 2003;60:531–538, 474.
- Anger WK, Liang YX, Nell V, et al. Lessons learned—15 years of the WHO-NCTB: a review. *Neurotoxicology*. 2000;21(5):837–846.
- Arcury TA, Quandt SA, Dearth A. Farmworker pesticide exposure and community-based participatory research: rationale and practical applications. *Environ Health Perspect*. 2001;109(suppl 3):429–434.
- Armstrong JM, Loer-Martin D, Leibnitz R. Developmental immunotoxicant exposure and exacerbated postnatal immune responses: asthma. In: Holladay SD, ed. *Developmental Immunotoxicology*. Boca Raton: CRC Press; 2005:229–281.
- Attig L, Gabory A, Junien C. Nutritional developmental epigenomics: immediate and long-lasting effects. *Proc Nutr Soc*. 2010;69:221–231.
- Baccarelli A, Bollati V. Epigenetics and environmental chemicals. *Curr Opin Pediatr*. 2009;21:243–251.
- Bailey GS, Reddy AP, Pereira CB, et al. Non-linear cancer response at ultra-low dose: a 40,800-animal ED001 tumor and biomarker study. *Chem Res Toxicol*. 2009;22:1264–1276.
- Bammler T, Beyer RP, Bhattacharya S, et al. Standardizing global gene expression analysis between laboratories and across platforms. *Nat Methods*. 2005;2:351–356.
- Barile FA. *Clinical Toxicology: Principles and Mechanisms*, 2nd ed. New York: Informa Healthcare; 2010.
- Barnes DG, Dourson M. Reference dose (RfD): description and use in health risk assessments. *Regul Toxicol Pharmacol*. 1988;8:471–486.
- Bartell SM, Takaro TK, Ponce RA, et al. Risk assessment and screening strategies for beryllium exposure. *Technology*. 2000;7:241–249.
- Bartels CF, James K, La Du BN. DNA mutations associated with the human butyrylcholinesterase J-variant. *Am J Hum Genet*. 1992;50:1104–1114.
- Beauchamp TL, Childress JF. *Principles of Biomedical Ethics*. 4th ed. New York: Oxford University Press; 1994.
- Bernal AJ, Jirtle RL. Epigenomic disruption: the effects of early developmental exposures. *Birth Defects Res A Clin Mol Teratol*. 2010;88(10):938–944.
- Bhagal N, Combes R. TGN1412: time to change the paradigm for the testing of new pharmaceuticals. *Altern Lab Anim*. 2006;34:225–239.
- Binder LM, Storzach D, Anger WK, et al. Subjective cognitive complaints, affective distress, and objective cognitive performance in Persian Gulf War veterans. *Arch Clin Neuropsychol*. 1999;14:531–536.
- Binder LM, Storzach D, Campbell KA, et al. Neurobehavioral deficits associated with chronic fatigue syndrome in veterans with Gulf War unexplained illnesses. *J Int Neuropsychol Soc*. 2001;7:835–839.
- Bliss CL. Some principles of bioassay. *Am Sci*. 1957;45:449–466.
- Bolon B, Garman R, Jensen K, Krinke G, Stuart B. A "best practices" approach to neuropathologic assessment in developmental neurotoxicity testing—for today. *Toxicol Pathol*. 2006;34(3):296–313.
- Boverhof DR, Zacharewski TR. Toxicogenomics in risk assessment: applications and needs. *Toxicol Sci*. 2006;89:352–360.
- Bruce RD. An up-and-down procedure for acute toxicity testing. *Fundam Appl Toxicol*. 1985;5:151–157.
- Bruce RD. A confirmatory study of the up-and-down method for acute oral toxicity testing. *Fundam Appl Toxicol*. 1987;8:97–100.
- Brusick DJ, Fields WR, Myhr BC, Doolittle DJ. Genetic toxicology. In: Hayes AW, ed. *Principles and Methods of Toxicology*. 5th ed. New York: Informa Healthcare; 2008:1179–1222:chap 23.
- Burbacher TM, Grant KS. Methods for studying nonhuman primates in neurobehavioral toxicology and teratology. *Neurotoxicol Teratol*. 2000;22:475–486.
- Burbacher TM, Grant KS, Mayfield DB, et al. Prenatal methylmercury exposure affects spatial vision in adult monkeys. *Toxicol Appl Pharmacol*. 2005;208:21–28.
- Calabrese EJ, Blain R. The occurrence of hormetic dose responses in the toxicological literature, the hormesis database: an overview. *Toxicol Appl Pharmacol*. 2005;202:289–301.
- Callahan D, Jennings B. Ethics and public health: forging a strong relationship. *Am J Public Health*. 2002;92:169–176.
- Carson R. *Silent Spring*. Boston: Houghton Mifflin; 2002, c 1962.
- Cheng TF, Choudhuri S, Muldoon-Jacobs K. Epigenetic targets of some toxicologically relevant metals: a review of the literature. *J Appl Toxicol*. 2012;32(9):643–653.
- Christian MS. Test methods for assessing female reproductive and developmental toxicology. In: Hayes AW, ed. *Principles and Methods of Toxicology*. 5th ed. New York: Informa Healthcare; 2008:1641–1712:chap 34.
- Claudio L. An analysis of the U.S. Environmental Protection Agency neurotoxicity testing guidelines. *Regul Toxicol Pharmacol*. 1992;16(2):202–212.
- Claudio L, Kwa WC, Russell AL, Wallinga D. Testing methods for developmental neurotoxicity of environmental chemicals. *Toxicol Appl Pharmacol*. 2000;164(1):1–14.
- Coble Y, Coussens C, Quinn K. *Environmental Health Sciences Decision Making: Risk Management, Evidence, and Ethics: Workshop Summary*. Washington, DC: National Academies Press; 2009.
- Cohen SM. Cell proliferation and carcinogenesis. *Drug Metab Rev*. 1998;30:339–357.
- Cohen SM. Calcium phosphate-containing urinary precipitate in rat urinary bladder carcinogenesis. *IARC Sci Publ*. 1999;147:175–189.
- Corburn J. Environmental justice, local knowledge, and risk: the discourse of a community-based cumulative exposure assessment. *Environ Manage*. 2002;29:451–466.
- Cory-Slechta DA. Relationships between lead-induced learning impairments and changes in dopaminergic, cholinergic, and glutamatergic neurotransmitter system functions. *Annu Rev Pharmacol Toxicol*. 1995;35:391–415.
- Cory-Slechta DA. Legacy of lead exposure: consequences for the central nervous system. *Otolaryngol Head Neck Surg*. 1996;114:224–226.



- Cory-Slechta DA. Lead-induced impairments in complex cognitive function: offerings from experimental studies. *Child Neuropsychol*. 2003;9:54-75.
- Cory-Slechta DA, Clayton KM, Foran JA, et al. Methods to identify and characterize developmental neurotoxicity for human health risk assessment. I: behavioral effects. *Environ Health Perspect*. 2001;109(suppl 1):79-91.
- Costa LG, Eaton DL. *Gene-Environment Interactions: Fundamentals of Epigenetics*. New York: Wiley Press; 2006:557 pp.
- Croup RS. An improved procedure for low-dose carcinogenic risk assessment from animal data. *J Environ Pathol Toxicol Oncol*. 1984;3:339-348.
- Cummings JA, Clemens LG, Nunes AA. Mother counts: how effects of environmental contaminants on maternal care could affect the offspring and future generations. *Front Neuroendocrinol*. 2010;31:440-451.
- D'Arcy PF, Barron DWG, eds. *Proceedings of the First International Conference on Harmonisation*. Belfast: Queen's University of Belfast; 1992.
- Donovan CE, Finn PW. Immune mechanisms of childhood asthma. *Thorax*. 1999;54:938-946.
- Dorman DC, Allen SL, Hyczkowski JZ, et al. Methods to identify and characterize developmental neurotoxicity for human health risk assessment. III: pharmacokinetic and pharmacodynamic considerations. *Environ Health Perspect*. 2001;109(suppl 1):101-111.
- Doull J. Factors influencing toxicity. In: Doull J, Klaassen CD, Amis MG, eds. *Casaretti and Doull's Toxicology: The Basic Science of Poisons*. 2nd ed. New York: Macmillan; 1980:70-83.
- Dybing E, Sanner T. Species differences in chemical carcinogenesis of the thyroid gland, kidney and urinary bladder. *IARC Sci Publ*. 1999;147:15-32.
- Eaton DL. Scientific judgment and toxic torts: a primer in toxicology for judges and lawyers. *J Law Policy*. 2003;12:9-42.
- Eaton DL, Gallagher EP. Introduction to principles of toxicology. In: McQueen C, ed. *Comprehensive Toxicology: Volume 1, General Principles*. 2nd ed. New York: Elsevier; 2010:1-46.
- Elman KD, Moser VC. Evaluation of cognitive function in weanling rats: a review of methods suitable for chemical screening. *Neurotoxicol Teratol*. 2006;28(1):144-161.
- Eichbaum M, Ingelman-Sundberg M, Evans WE. Pharmacogenomics and individualized drug therapy. *Annu Rev Med*. 2006;57:119-137.
- EPA. *Health Effects Test Guidelines*. OPPTS 870.6300, Developmental Neurotoxicity Toxicity Study. Washington, DC: U.S. Environmental Protection Agency; 1998.
- EPA. *Environmental Justice*. Washington, DC: Environmental Protection Agency; 2005. Available at: <http://www.epa.gov/compliance/environmentaljustice/>.
- Farahat TM, Abdelrasoul GM, Amir MM, et al. Neurobehavioural effects among workers occupationally exposed to organophosphorus pesticides. *Occup Environ Med*. 2003;60:279-286.
- Faustman EM. Short-term tests for teratogens. *Statist Res*. 1985;205:355-364.
- Faustman EM, Allen BC, Kaylock RJ, et al. Dose-response assessment for developmental toxicity. I. Characterization of database and determination of no observed adverse effect levels. *Fundam Appl Toxicol*. 1994;21:478-486.
- Feldt O. Metabolomics—the link between genotypes and phenotypes. *Plant Mol Biol*. 2002;48:155-171.
- Finney DJ. *Probit Analysis*. Cambridge: Cambridge University Press; 1971.
- Finney DJ. The median lethal dose and its estimation. *Arch Toxicol*. 1985;56:215-218.
- Gail A, Schiestl RB. Cell division transforms mutagenic lesions into deletion-recombination lesions in yeast cells. *Mutat Res*. 1999;429:13-26.
- Gao X. Construction of null statistics in permutation-based multiple testing for multi-factorial microarray experiments. *Bioinformatics*. 2006;22:1486-1494.
- Gartman RH, Fox AS, Jormer BS, et al. Methods to identify and characterize developmental neurotoxicity for human health risk assessment. II: neuropathology. *Environ Health Perspect*. 2001;109(suppl 1):93-100.
- Gilbert G. Ethical, legal, and social issues: our children's future. *Neurotoxicology*. 2005a;26:521-530.
- Gilbert SG. Public health and the precautionary principle. *Northwest Public Health*. 2005b;spring/summer;2.
- Gilbert SG. Supplementing the traditional institutional review board with an environmental health and community review board. *Environ Health Perspect*. 2006;114:1626-1629.
- Gilbert SG, Eaton DL. Ethical, legal, social, and professional issues in toxicology. In: Ballantyne B, Morris TC, Syversen T, eds. *General and Applied Toxicology*. 3rd ed. West Sussex, UK: Wiley; 2009:chap 116.
- Glynn P, Read DJ, Lush MJ, et al. Molecular cloning of neuropathy target esterase (NTE). *Chem Biol Interact*. 1999;119(120):513-517.
- Goldfrey KM, Sheppard A, Gluckman PD, et al. Epigenetic gene promoter methylation at birth is associated with child's later adiposity. *Diabetes*. 2011;60:1528-1534.
- Goldstein A, Aronow L, Kalman SM. *Principles of Drug Action*. New York: Wiley; 1974.
- Goldstein BD. The precautionary principle: is it a threat to toxicological science? *Int J Toxicol*. 2006;25:3-7.
- Goodman JL, Augustine KA, Cunningham ML, et al. What do we need to know prior to thinking about incorporating an epigenetic evaluation into safety assessments? *Toxicol Sci*. 2010;116:375-381.
- Grosser M. *Unrevealed: Non-Disclosure of Conflicts of Interest in Four Leading Medical and Scientific Journals*. Washington, DC: Center for Science in the Public Interest; 2004.
- Grisham JW. Interspecies comparison of liver carcinogenesis: implications for cancer risk assessment. *Carcinogenesis*. 1997;18:59-81.
- Goodman PS, Victoroff MS, Holmes NC, et al. Evidence-based toxicology: a comprehensive framework for causation. *Hum Exp Toxicol*. 2005;24:161-201.
- Halle W. The Registry of Cytotoxicity: toxicity testing in cell cultures to predict acute toxicity (LD50) and to reduce testing in animals. *Altern Lab Anim*. 2003;31(2):69-198.
- Hanna EZ, Chou SP, Grant BF. The relationship between drinking and heart disease morbidity in the United States: results from the National Health Interview Survey. *Alcohol Clin Exp Res*. 1997;21:111-119.
- Harkness JE, Wagner JE. *The Biology and Medicine of Rabbits and Rodents*. 4th ed. New York: Williams and Wilkins; 1995.
- Haseeman JK. Issues in carcinogenicity testing: dose selection. *Fundam Appl Toxicol*. 1985;5:66-78.
- Haich EE, Palmer IR, Thuss-Erdost L, et al. Cancer risk in women exposed to diethylstilbestrol in utero. *JAMA*. 1998;280:630-634.
- Hayes AW, ed. *Principles and Methods of Toxicology*. 5th ed. New York: Informa Healthcare; 2008.
- Hayes RB, Patrick E, Maibach HI. Dermatotoxicology. In: Hayes AW, ed. *Principles and Methods of Toxicology*. New York: Informa Healthcare; 2008:1359-1406:chap 27.
- Head JA, Dolinoy DC, Basu N. Epigenetics for ecotoxicologists. *Environ Toxicol Chem*. 2012;31(2):221-227.
- Hengstler IG, Van der Burg B, Steinberg P, et al. Interspecies differences in cancer susceptibility and toxicity. *Drug Metab Rev*. 1999;31:917-970.
- Hill AB. The environment and disease: association or causation? *Proc R Soc Med*. 1965;58:295-300.
- Holladay SD, ed. *Developmental Immunotoxicology*. Boca Raton: CRC Press; 2005:464.
- Holliday R. Epigenetics: a historical overview. *Epigenetics*. 2006;1:76-80.
- Huff JE. Value, validity, and historical development of carcinogenesis studies for predicting and confirming carcinogenic risk to humans. In: Kitchin KT, ed. *Carcinogenicity Testing: Predicting & Interpreting Chemical Effects*. New York: Marcel Dekker; 1999:21-123.
- Ikeida T. Drug-induced idiosyncratic hepatotoxicity: prevention strategy developed after the troglitazone case. *Drug Metab Pharmacokinet*. 2011;26(1):60-70.
- Irwil S. Comprehensive observational assessment. Ia. A systematic, quantitative procedure for assessing the behavioral and physiologic state of the mouse. *Psychopharmacologia*. 1968;13(5):222-237.
- Jacobson-Krato D, Keller KA. *Toxicology Testing Handbook: Principles, Applications and Data Interpretation*. 2nd ed. New York: Informa Healthcare; 2006.
- Kamel F, Rowland AS, Park LP, et al. Neurobehavioral performance and work experience in Florida farmworkers. *Environ Health Perspect*. 2003;111:1765-1772.



- East NE. An ethics framework for public health. *Am J Public Health*. 2001;91:1776-1782.
- Kilman CR, Swenberg LM, Meek ME, Gargas ML. Assessing the dose-dependency of allometric scaling performance using physiologically based pharmacokinetic modeling. *Regul Toxicol Pharmacol*. 2003;38(3):345-367.
- Kobayashi Y, Fukumaki Y, Yabuta T, et al. Sirtin-protin replacement at residue 127 of NADH-cytochrome b5 reductase causes hereditary methemoglobinemia, generalized type. *Blood*. 1990;75:1408-1413.
- Krimsky S, Rothenberg LS. Conflicts of interest policies in science and medical journals: editorial practices and author disclosures. *Sci Eng Ethics*. 2001;7:205-218.
- Krimsky S, Sweet E. An analysis of industry and medical journal conflict-of-interest policies. *Account Res*. 2009;16:235-253.
- Krueger M. How omics technologies can contribute to the "3R" principles by introducing new strategies in animal testing. *Trends Biotechnol*. 2006;24:343-346.
- Landrigan PJ, Schecter CB, Lipson JM, et al. Environmental pollutants and disease in American children: estimates of morbidity, mortality, and costs for lead poisoning, asthma, cancer, and developmental disabilities. *Environ Health Perspect*. 2002;110:721-728.
- Langham BP, Harmon R, Khoury T, et al. Low-level environmental lead exposure and children's intellectual function: an international pooled analysis. *Environ Health Perspect*. 2005;113:894-899.
- Lary JM, Daniel KL, Erickson JD, et al. The return of thalidomide: can birth defects be prevented? *Drug Saf*. 1999;21:161-169.
- Layner TL, Barone S Jr, Moser VC, Padilla S. Gestational exposure to chlorpyrifos: dose-response profiles for cholinesterase and carboxylesterase activity. *Toxicol Sci*. 1999;52:92-100.
- Lo K, McLennan WG, Williams DP, Howard CV. Synergistic interactions between commonly used food additives in a developmental neurotoxicity test. *Toxicol Sci*. 2006;90:178-187.
- LeBaron MJ, Rasoulpour RF, Klapacz J, et al. Epigenetics and chemical safety assessment. *Mutat Res*. 2010;705(1):83-95.
- Lo K. Environmental justice: building a unified vision of health and the environment. *Environ Health Perspect*. 2002;110(suppl 2):141-144.
- Leimann-McKreman LD, Caudill D. Biochemical basis for mouse resistance to hyaline droplet nephropathy: lack of relevance of the alpha 2u-globulin protein superfamily in this male rat-specific syndrome. *Toxicol Appl Pharmacol*. 1992;112:214-221.
- Lengold A. *A Small Country Almanac: With Essays on Crossbreeding*. Oxford: Oxford University Press; 1949 [reprinted, 2001].
- Levine RR. *Pharmacology: Drug Actions and Reactions*. Boston: Little, Brown, and Company; 1978.
- Limden JC, Holmes E, Nicholson JK. Metabonomics techniques and applications to pharmaceutical research & development. *Pharm Res*. 2006;23:1075-1088.
- Lindon JC, Nicholson JK, Holmes E, et al. Contemporary issues in toxicology: the role of metabolomics in toxicology and its evaluation by the COMET project. *Toxicol Appl Pharmacol*. 2003;187:137-146.
- Litchfield JT, Wilcoxon E. Simplified method of evaluating dose-effect experiments. *J Pharmacol Exp Ther*. 1949;96:99-113.
- Litchfield JT. A method for rapid graphic solution of time-percent effective curve. *J Pharmacol Exp Ther*. 1949;97:399-408.
- Littenfeld NA, Farmer JEL, Gaylar DW, et al. Effects of dose and time in a long-term, low-dose carcinogenicity study. In: Straff JA, Muhlman MA, eds. *Innovations in Cancer Risk Assessment (EPA) Study*. Park Forest South, IL: Patholox Publishers; 1979.
- Luster MI, Dean JH, Germolec DR. Consensus workshop on methods to evaluate developmental immunotoxicity. *Environ Health Perspect*. 2003;111:579-583.
- Maggioli J, Hoover A, Wang L. Toxicogenomic analysis methods for predictive toxicology. *J Pharmacol Toxicol Methods*. 2006;53:31-37.
- Marcobianchi G. From general policy to legal rule: aspirations and limitations of the precautionary principle. *Environ Health Perspect*. 2003;111:1799-1803.
- Maurissen JP, Gilbert SG, Sander M, et al. Workshop proceedings: managing conflict of interest in science. A little consensus and a lot of controversy. *Toxicol Sci*. 2005;87:1-14.
- McCauley LA, Anger WK, Keifer M, et al. Studying health outcomes in farmworker populations exposed to pesticides. *Environ Health Perspect*. 2006;114:953-960.
- Milesop BE, Ferenc SA. Methods to identify and characterize developmental neurotoxicity for human health risk assessment: overview. *Environ Health Perspect*. 2001;109(suppl 1):77-78.
- Mohr LC, Rodgers JK, Silvestri GA. Glutathione S-transferase M1 polymorphism and the risk of lung cancer. *Anticancer Res*. 2003;23:2111-2124.
- Montbellin TM, Morgan KT. Chemically-induced nasal carcinogenesis and epithelial cell proliferation: a brief review. *Mutat Res*. 1997;380:33-41.
- Montello-Prosch R, Pastor M Jr, Fornas C, Sadd J. Environmental justice and inequality in southern California: implications for future research. *Environ Health Perspect*. 2002;110(suppl 2):149-154.
- Moser VC. The functional observational battery in adult and developing rats. *Neurotoxicology*. 2000;21(6):989-996.
- Moser VC, Simmons JE, Germolec C. Neurotoxicological interactions of a five-pesticide mixture in preweanling rats. *Toxicol Sci*. 2006;92:235-245.
- Myers GJ, Davidson PW, Cox C, et al. Twenty-seven years studying the human neurotoxicity of methylmercury exposure. *Environ Res*. 2000;85:275-285.
- Myers NJ, Rattensperger C, eds. *Precautionary Tools for Reshaping Environmental Policy*. Cambridge: MIT Press; 2006.
- NAS. *Policy on Committee Composition and Balance and Conflicts of Interest for Committees Used in the Development of Reports*. Washington, DC: National Academies Press; 2003.
- NAS/NRC. *Toxicity Testing in the 21st Century: A Vision and a Strategy*. Washington, DC: National Academy Press; 2007.
- NAS/NRC. *Toxicity-Pathway-Based Risk Assessment: Preparing for Paradigm Change: A Symposium Summary*. Washington, DC: National Academies Press; 2010.
- Needleman HL, Bellinger D. The health effects of low level exposure to lead. *Annu Rev Public Health*. 1991;12:111-140.
- Netzlaff F, Lefé CM, Wertz PW, Schaefer UE. The human epidermis models: EpiSkin, SkinEthic and EpiDerm: an evaluation of morphology and their suitability for testing phototoxicity, irritation, corrosivity, and substance transport. *Eur J Pharm Biopharm*. 2005;60(2):167-178.
- Nwake UC. A framework for integrating environmental justice in regulatory analysis. *Int J Environ Res Public Health*. 2011;8(6):2366-2385.
- Nystrom M, Mutanen M. Diet and epigenetics in colon cancer. *World J Gastroenterol*. 2009;15:257-263.
- OECD. *Draft Guidance Document on Reproductive Toxicity Testing and Assessment, Series on Testing and Assessment No. 43*. Paris, France: Environment Directorate, Organisation for Economic Cooperation and Development; 2004.
- O'Fallon LR, Deary A. Community-based participatory research as a tool to advance environmental health sciences. *Environ Health Perspect*. 2002;110(suppl 2):155-159.
- Pan Z, Raloff D. Comparing and combining NMR spectroscopy and mass spectrometry in metabolomics. *Anal Bioanal Chem*. 2007;387(2):525-527.
- Perez F, Herbarman J. Prenatal environmental exposures, epigenetics, and disease. *Reprod Toxicol*. 2011;31:363-373.
- Peterson M. The precautionary principle is incoherent. *Risk Anal*. 2006;26:595-601.
- Pugsley MK, Authier S, Curtis MJ. Principles of safety pharmacology. *Br J Pharmacol*. 2008;154(7):1582-1599.
- Pugsley MK, Towart R, Authier S, Gallacher DJ, Curtis MJ. Innovations in safety pharmacology testing. *J Pharmacol Toxicol Methods*. 2011;64(1):1-6.
- Rattensperger C, Dickner J, eds. *Protecting Public Health & the Environment: Implementing the Precautionary Principle*. Washington, DC: Island Press; 1999.
- Rodfem WS, Strouk J, Storey S, et al. Spectrum of effects detected in the rat functional observational battery following oral administration of some CNS targeted compounds. *J Pharmacol Toxicol Methods*. 2005;52:77-82.
- Road PE. Carcinogenicity studies. In: Sipes IG, McQueen CA, Gandolfi A, eds. *Comprehensive Toxicology* (Williams PD, Houtendorf D, eds. *Toxicological Testing and Evaluation*, Vol. 2. New York: Pergamon Press; 1997:121-131.



- Rhombert LR, Wolff SK. Empirical scaling of single oral lethal doses across mammalian species based on a large database. *Risk Anal.* 1998;18:741-753.
- Rice DC. Neurotoxicity of lead, methylmercury, and PCBs in relation to the Great Lakes. *Environ Health Perspect.* 1995;103(suppl 9):71-87.
- Rice DC, Gilbert SG. Early chronic low-level methylmercury poisoning in monkeys impairs spatial vision. *Science.* 1982;216(4547):759-761.
- Rice DC, Gilbert SG. Exposure to methyl mercury from birth to adulthood impairs high-frequency hearing in monkeys. *Toxicol Appl Pharmacol.* 1992;115:6-10.
- Rice DC, Gilbert SG. Effects of developmental methylmercury exposure or lifetime lead exposure on vibration sensitivity function in monkeys. *Toxicol Appl Pharmacol.* 1995;134:161-169.
- Roberts RA. Peroxisome proliferators: mechanisms of adverse effects in rodents and molecular basis for species differences. *Arch Toxicol.* 1999;73:413-418.
- Rodricks JV, Gaylor DW, Turnbull D. Quantitative extrapolations in toxicology. In: Hayes AW, ed. *Principles and Methods in Toxicology*. 5th ed. New York: Informa Healthcare; 2008:453-474:chap 9.
- Rohlfman DS, Anger WK, Tamulinas A, et al. Development of a neurobehavioral battery for children exposed to neurotoxic chemicals. *Neurotoxicology.* 2001a;22:657-665.
- Rohlfman DS, Bailey SR, Anger WK, McCauley L. Assessment of neurobehavioral function with computerized tests in a population of Hispanic adolescents working in agriculture. *Environ Res.* 2001b;85:14-24.
- Rohlfman DS, Gimenez LS, Eckerman DA, et al. Development of the Behavioral Assessment and Research System (BARS) to detect and characterize neurotoxicity in humans. *Neurotoxicology.* 2003;24:523-531.
- Rosenfeld CS. Animal models to study environmental epigenetics. *Biol Reprod.* 2010;82:473-488.
- Rush RE, Bonnette KL, Douds DA, et al. Dermal irritation and sensitization. In: Derelanko MJ, Hollinger MA, eds. *CRC Handbook of Toxicology*. New York: CRC Press; 1995:105-162.
- Simon T. Just who is at risk? The ethics of environmental regulation. *Hum Exp Toxicol.* 2011;30:795-819.
- Skinner MK. Role of epigenetics in developmental biology and transgenerational inheritance. *Birth Defects Res C Embryo Today.* 2011;93:51-55.
- Storey JD, Xiao W, Leek JT, et al. Significance analysis of time course microarray experiments. *Proc Natl Acad Sci U S A.* 2005;102:12837-12842.
- Szyf M. The dynamic epigenome and its implications in toxicology. *Toxicol Sci.* 2007;100(1):7-23.
- Tennant RW, Stasiewicz S, Mennear J, et al. Genetically altered mouse models for identifying carcinogens. *MRC Sci Publ.* 1999;146:123-150.
- Tiffany-Castiglioni E, ed. *In Vitro Neurotoxicology: Principles and Challenges (Methods in Pharmacology and Toxicology)*. Totowa, NJ: Humana Press; 2004.
- Travis CC, White RK. Interspecific scaling of toxicity data. *Risk Anal.* 1988;8:119-125.
- Uetrecht J. Idiosyncratic drug reactions: current understanding. *Annu Rev Pharmacol Toxicol.* 2007;47:513-539.
- Uhl K, Cox E, Rogan R, et al. Thalidomide use in the US: experience with pregnancy testing in the S.T.E.P.S. programme. *Drug Saf.* 2006;29:321-329.
- Ukalsis U, Kramer PJ, Otejczyk K, Mueller SO. Replacement of in vivo acute oral toxicity studies by in vitro cytotoxicity methods: opportunities, limits and regulatory status. *Regul Toxicol Pharmacol.* 2008;51(1):108-118.
- Vandegheuchte MB, Janssen CR. Epigenetics and its implications for ecotoxicology. *Ecotoxicology.* 2011;20:607-624.
- Vandenberg LN, Maffini MV, Sonnenschein C, Rabin BS, Soto AM. Bisphenol-A and the great divide: a review of controversies in the field of endocrine disruption. *Endocr Rev.* 2009;30(1):75-95.
- Wang L, McLeod HL, Weinshilboum RM. Genomics and drug response. *N Engl J Med.* 2011;364(12):1144-1153.
- Waters MD, Foster JM. Toxicogenomics and systems toxicology: aims and prospects. *Nat Rev Genet.* 2004;5:936-948.
- Watson RE, Goodman JL. Epigenetics and DNA methylation come of age in toxicology. *Toxicol Sci.* 2002;67:11-16.
- Weil C. Tables for convenient calculation of median-effective dose (LD50 or ED50) and instruction in their use. *Biometrics.* 1952;8:249-263.
- Weinshilboum RM, Ornteress DM, Szumlanski CL. Methylation pharmacogenetics: catechol O-methyltransferase, thiopurine methyltransferase, and histamine N-methyltransferase. *Annu Rev Pharmacol Toxicol.* 1999;39:19-52.
- Weston AD, Hood L. Systems biology, proteomics, and the future of health care: toward predictive, preventative, and personalized medicine. *J Proteome Res.* 2004;3:179-196.
- Williams DE. The rainbow trout liver cancer model: response to environmental chemicals and studies on promotion and chemoprevention. *Comp Biochem Physiol C Toxicol Pharmacol.* 2012;155(1):121-127.
- Williams DE, Ormer G, Willard KD, et al. Rainbow trout (*Oncorhynchus mykiss*) and ultra-low dose cancer studies. *Comp Biochem Physiol C Toxicol Pharmacol.* 2009a;149(2):175-181.
- Williams ES, Panko J, Paustebach DI. The European Union's REACH regulation: a review of its history and requirements. *Crit Rev Toxicol.* 2009b;39(7):553-575.
- Wilson NH, Hardisty IF, Hayes JR. Short-term, subchronic and chronic toxicology studies. In: Hayes AW, ed. *Principles and Methods of Toxicology*. New York: Informa Healthcare; 2008:1223-1264:chap 24.
- Wiman KG. The retinoblastoma gene: role in cell cycle control and cell differentiation. *FASEB J.* 1993;7:841-845.
- Wogan GN, Pagliaronga S, Newberne PM. Carcinogenic effects of low dietary levels of aflatoxin B1 in rats. *Food Cosmet Toxicol.* 1974;12:681-685.
- Youngson NA, Whitelaw E. Transgenerational epigenetic effects. *Annu Rev Genomics Hum Genet.* 2008;9:233-257.
- Zhang X, Ho SM. Epigenetics meets endocrinology. *J Mol Endocrinol.* 2011;46(R):1-R32.